THE SYNTHESIS OF DRUGS OF POTENTIAL ANTIMALARIAL AND AMOEBICIDAL ACTIVITY DERIVED FROM LINEAR BENZQUINOLINES, PYRIDOQUINOLINES AND BENZACRIDINES,

by

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Thesis presented for the degree of
Ph.D.
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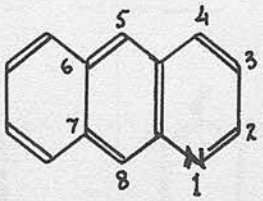
CONTENTS.

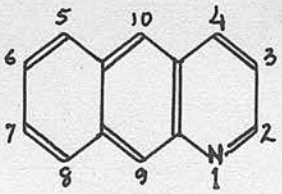
NOMENCLATURE and NUMBERING.

Linear benzquinoline derivatives.

As 6:7-benzquinoline has also been referred to as 1-azanthracene in the course of this thesis, two methods of numbering have been used — [A] and [B] respectively.



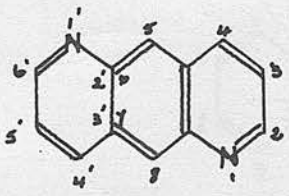
[A]



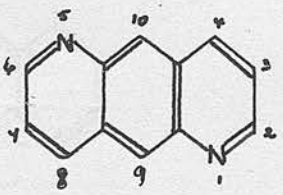
[B]

Linear pyridoquinoline derivatives.

The two linear pyridoquinolines — $6:7:2^1:3^1$ and $6:7:3^1:2^1$-pyridoquinolines — [A] and [B] -have also been described as 1:5- and 1:8-anthrazolines - [C] and [D] - and numbered thus -



[A]



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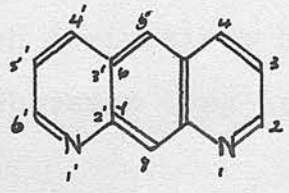
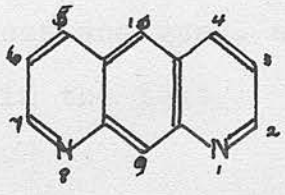


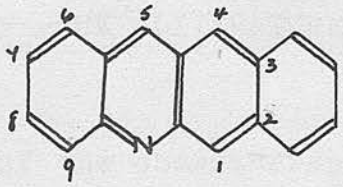
[B]



[D]

Linear benzacridine derivatives.

The numbering of the linear benzacridine nucleus used in this thesis is as follows:-



All new compounds which have been analysed, or of which derivatives have been analysed, are underlined wherever they appear in the text.

I. INTRODUCTION AND GENERAL SURVEY OF THE LITERATURE.

The history of the chemotherapy of malaria typifies the history of chemotherapy in general. The old empiricism has been supplemented by definite, though not always successful, attempts to correlate the specific action of drugs on parasites with chemical constitution, and interpret their effect in terms of molecular structure. This approach has proved inadequate, however, and recently, much attention has been focussed on biochemical considerations such as substrate competition and enzyme inhibition. Whether this new line of research will lead to a rational theory of chemotherapeutic activity and the discovery of novel chemotherapeutic agents is a matter of conjecture, which will only be realised at some future date.

Malaria is the most persistent, destructive and widespread of all tropical diseases. Always a grave social problem in tropical and subtropical countries, the malarial incidence in the Far East campaign of World War II, and the return home of Allied soldiers, a large proportion of whom were carriers of the disease, made Britain and America "malaria conscious".

As a result, research on the chemotherapy of malaria was stimulated to a very marked degree; some idea of the extensive work which was carried out in America alone may be obtained from the Survey of Antimalarial Compounds published by the American Government in 1947, a comprehensive index of over twelve thousand compounds tested for antimalarial activity. Two British chemists, however, Curd and Rose, with the discovery of paludrine, produced what has proved to be the greatest advance in synthetic antimalarials in recent years. Though by no means a complete answer to the malarial problem, it constitutes a direct break with traditional lines of research, and has opened up new fields to chemists to investigate and explore.

The presence of parasites in the blood of patients suffering from malaria was demonstrated by Laveran in 1880. Fifteen years later, Mason and Ross proved that the infecting vector was the anopheline mosquito, the parasite having a sexual existence in the mosquito and an asexual existence in certain vertebrates. In man, there are three main forms of malarial infections - benign tertian which is caused by Plasmodium vivax, quartan malaria caused by Plasmodium malariae, and malignant tertian or subtertian caused by Plasmodium falciparum. Although

the differences between these three forms have proved of extreme importance in the practical treatment of the disease, the various stages in the life cycle of the three plasmodia are essentially similar.

When an infected mosquito bites its victim, a large number of rod-shaped parasites, known as sporozoites, are injected into the blood stream. Eventually they invade the red blood cells, becoming trophozoites, where they grow, divide and re-enter the blood stream, producing the chill and fever characteristic of the disease. These merozoites, as they are now called, may enter fresh erythrocytes and repeat this process, or develop into sexual forms or gametocytes, which produce no further malarial symptoms, but which, when taken into the stomach of a female mosquito, enter upon the sexual stage of the life-cycle.

The fate of the parasite in the interval between the bite of the mosquito and the blood stages of the infection has been the subject of much recent research. The great differences between infections produced by inoculation with infected blood and those induced by sporozoites, led James and Tate (1931) to postulate that the sporozoite underwent some development in the tissues before invading the blood cells. The actual discovery of exo-erythrocytic tissue

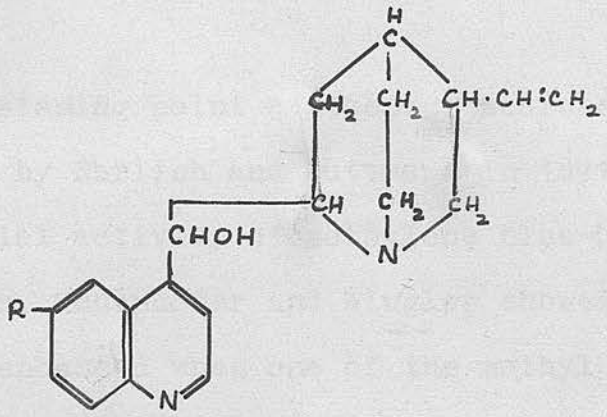
forms of P. gallinaceum infections in chicks was announced by James and Tate (1938) and since then, Huff and Coulston (1943) have worked out in detail the sequence of events for this period of the infection. The corresponding forms in monkeys were discovered by Shortt and Garnham (1948), and confirmed by Hawking et al (1948). Shortt, Garnham, Covell and Shute (1948) have also found exo-erythrocytic forms of P. vivax in human malaria in the liver of a patient, seven days after infection. Strong presumptive evidence for the existence of such forms in human malaria is available, based on prophylactic and curative studies of the disease. The inability to obtain radical cures of relapsing tertian malaria, due, probably, to the failure of the antimalarial drugs to penetrate and exert a lethal action on the tissue stages of the plasmodia, is in contrast to the ease by which it is possible to cure benign tertian malaria in paretics who have been infected by inoculation with parasitized blood.

From the above account of the life-cycle of the malaria parasite, it will be seen that there are two methods of attacking the disease, either to kill the parasite in the human patient, or to destroy the insect vector. Until recently, the only method of combating the mosquito was to cover the surface of

pools used as breeding places with oil, and so destroy the larvae. This is a very costly procedure and one difficult to carry out thoroughly. With the introduction of D.D.T., however, the mosquito became a very vulnerable target, and extensive use was made of it during the war, causing a decisive fall in the number of infected cases. Insect repellants, such as dimethyl phthalate, have also been used extensively and with considerable success.

The antimalarial problem, once the parasite has entered on its asexual existence, is governed by the various stages in its life-cycle. There are three possible points of attack - the sporozoite, the exo-erythrocytic forms, and the schizont stages of the blood phase. Since clinical symptoms are closely associated with the fission of the schizonts, early chemotherapeutic work was concentrated entirely on this part of the life-cycle, and a search for drugs which would eradicate parasites before the blood phase was reached and so constitute a true causal prophylactic, was neglected.

Cinchona bark was known in Europe as an effective treatment for malaria from the sixteenth century, but it was not until 1820 that Pelletier and Caventou isolated quinine (I) and conchinine (II), and identified them as the active principles of the bark. Cinchonine



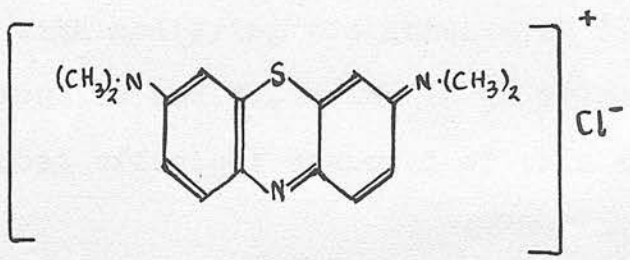
(I) (R = OCH_3)

(II) (R = H)

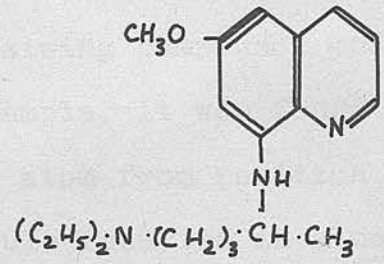
Rabe, in 1908, postulated the now accepted structure of quinine, which resisted all attempts at synthesis until Woodward and Doering achieved success in 1945. Their synthesis, however, is so complicated, and the yield so poor, that it is of no practical importance from the manufacturing point of view.

Quinine is a satisfactory clinical suppressive for malaria, but has no action on the exo-erythrocytic forms of the parasite. As early work was directed towards finding a substitute for quinine, it is not surprising that drugs which would completely eradicate malaria from the system were not forthcoming. Most of the early synthetic work was done in Germany, culminating in the discovery of plasmoquine and mepacrine, which, until the recent discovery of paludrine, were the main drugs, besides quinine, used in the clinical treatment of malaria.

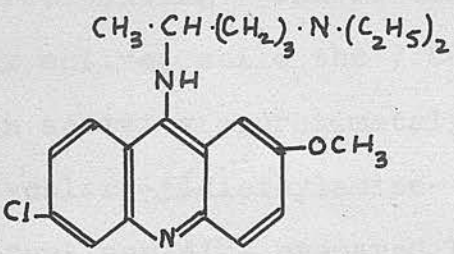
The starting point of these researches was the discovery by Ehrlich and Guttmann in 1891 of the antimalarial activity of methylene blue (III). Schülemann, Schönhöfer and Wingler showed that activity was enhanced when one of the methyl groups was replaced by a diethyl aminoethyl side chain. As this type of compound still possessed the definite characteristics of a dye-stuff, attention was directed towards quinoline derivatives carrying similar basic groups. This work resulted in the discovery of plasmoquine (IV) - 6-methoxy-8-(δ -diethylamino-α -methylbutylamino)-quinoline - which is highly active against the gametocytes of the malaria parasite. A review of the steps leading to the discovery of plasmoquine is given by Schülemann in Proc. Roy. Soc. Med. 1932. The high toxicity of this drug, however, limits its usefulness, so Mauss and Mietzch (1933), pursuing a similar line of research in the acridine series, synthesised mepacrine (V) — 8-chloro-3-methoxy-5-(δ -diethylamino-α -methylbutylamino)-acridine.



(III)



(IV)



(V)

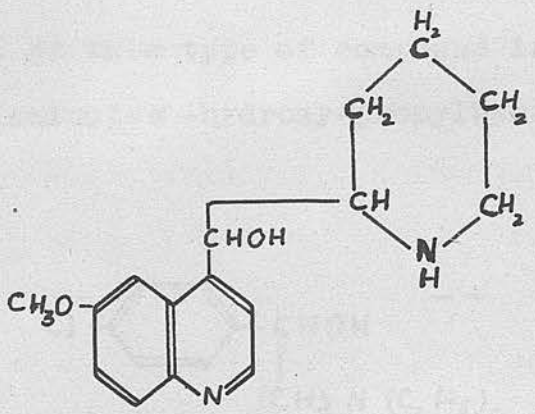
These two compounds, developed from the same viewpoint, appear to have essentially different modes of action. Thus while the chief value of plasmoquine lies in its powerful gametocidal action, mepacrine, like quinine, acts chiefly on the schizogenous stages of the parasite and has little, if any, effect on the gametocytes. Mepacrine has the advantage of being much less toxic than plasmoquine; they may be used conjointly with great effect in the treatment of malaria.

Until 1943, most of the antimalarial research was concerned with modifying the structures of quinine, plasmoquine and mepacrine in an attempt to discover the most efficient compound of this type,

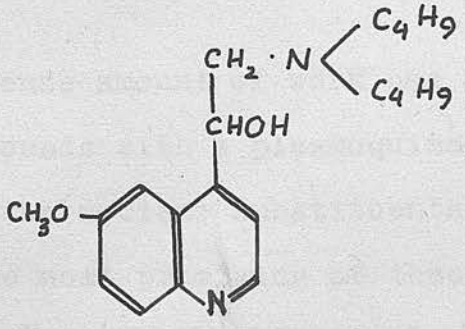
and with synthesising compounds modelled on these drugs. For example, it was found that the removal of the chlorine atom from position eight of the mepacrine molecule resulted in almost complete loss of activity. Feldmann and Kopeliowitzch (1935) found that the corresponding 7-chloro compound was only very slightly active, while the 7:8-dichloro compound showed an activity approximately half that of mepacrine. 9-chloro-5(δ-diethylamino-α-methyl-butylamino)-1- methyl acridine prepared by Hall and Turner (1945) was found to possess definite activity. Magidson and Grigorowsky (1933) investigated the effect of varying the length of the side chain; they found that chemotherapeutic activity was greatest using δ-diethylamino-n-butylamine. They also found that the introduction of a second methoxy group in position two of the mepacrine molecule yielded a product which was inactive, while a nitro group was more effective in the seven than in the eight position of the acridine nucleus.

considerable but not "almost complete"

Taking quinine as their model, King and co-workers (1938) have synthesised compounds showing activity against avian malaria, for example 4-(6[1]-methoxy-quinolyl)-α-piperidyl carbinol (VI) and dibutyl aminomethyl-6-methoxy-4-quinolyl carbinol (VII).



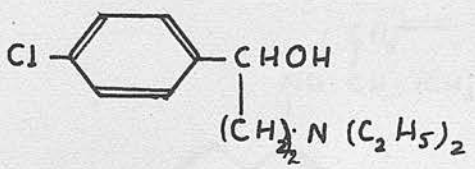
(VI)



(VII)

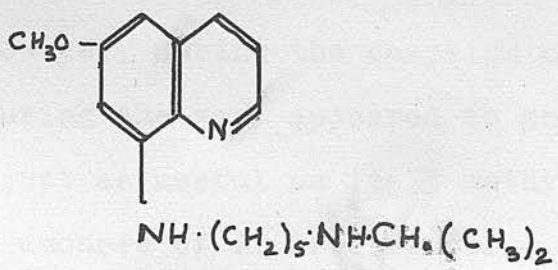
In these compounds the methoxy group is essential for activity, whereas, in the parent quinine, removal of the methoxy group has little or no effect on its antimalarial properties. Following up this work, a very large number of aromatic derivatives carrying a dialkylamino ethanol side chain have been prepared, many of which have been shown to possess activity against avian malaria. One of the simplest

examples of this type of compound is 4-chloro-γ-(dialkylamino)-α-hydroxy-propylbenzene (VIII).



(VIII)

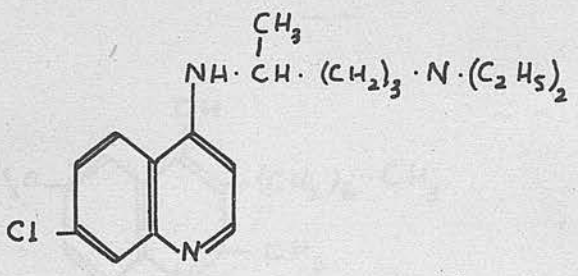
An immense amount of work has also been carried out on compounds with a plasmoquine-like structure, varying in the nuclear substituents and in the side chain. The most promising of these is pentaquin — 6-methoxy-8-(isopropyl-amino-amylamino)-quinoline (IX) prepared by Drake (1946).



(IX)

A large number of 4-amino-quinoline derivatives have been prepared, chiefly by I. G. Farbenindustrie, and tested for antimalarial activity. Of these,

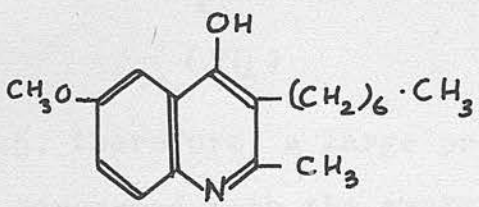
resochin or chloroquin (X) — 7-chloro-4-(δ-diethylamino-α-methylbutylamino)-quinoline — synthesised by Andersag and co-workers in 1935, is most notable.



(X)

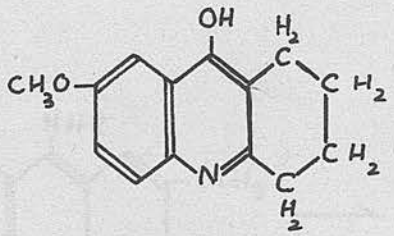
When chloroquin was first introduced, it was reported as being too toxic for practical use and was replaced by the 3-methyl analogue, known as sontochin, which was much less toxic and possessed an activity equivalent to that of mepacrine. A re-examination of the antimalarial properties of both these compounds, however, during the campaign carried out in America during the war, appeared to show that chloroquin was just as useful as its 3-methyl derivative, and large amounts of it are now being prepared commercially in the United States. Chloroquin is a more potent antimalarial than is mepacrine. It is found to be highly suppressive against acute attacks of vivax malaria, but has no causal prophylactic action and does not prevent relapse. It effects radical cure in cases of falciparum infections.

Another compound, worthy of mention, in so far that the side chain is non-basic and in the three position, is endochin (XI) — 2-methyl-4-hydroxy-6-methoxy-3-^{n}-heptyl quinoline.



(XI)

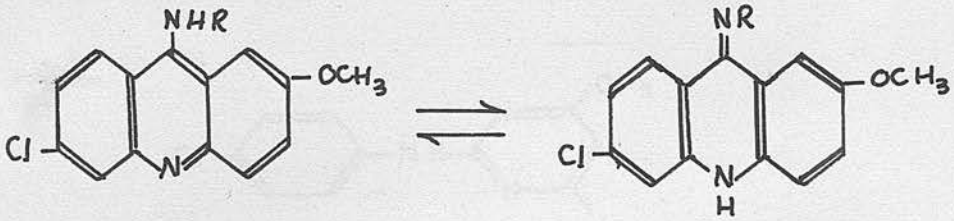
This compound was prepared by Salzer, a chemist at I. G. Farbenindustrie, in 1940, and reported as a causal prophylactic in avian malaria. It is interesting to note that removal of the methyl group reduces the activity to one twentieth of that shown by endochin itself. By twisting the side chain round into the form of a ring, a certain relationship may be observed between endochin and mepacrine. Stephen, Tonkin and Walker (1947) thus synthesised various tetrahydro-acridones, and found that 7-methoxy-1:2:3:4 tetrahydro-acridone (XII) was four times as active, on a weight basis, as endochin.



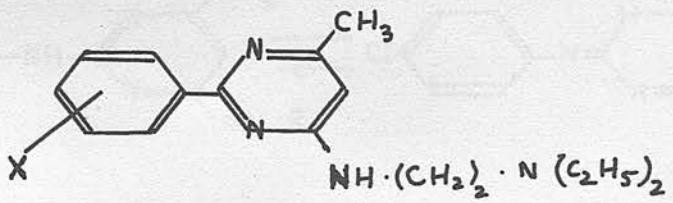
(XII)

Until 1945, therefore, a large proportion of the work had been concerned with the synthesis of quinoline derivatives resembling quinine, plasmoquine and mepacrine. The introduction by Curd, Davey and Rose of a biguanide derivative with an activity far surpassing any hitherto achieved thus heralded a new era in the chemotherapy of malaria. These workers decided to break with the traditional quinoline and acridine nucleus, and to investigate pyrimidine derivatives, since the latter are of great physiological importance and take part, as components of certain nucleoproteins, in a number of fundamental biological processes.

In 1942, Schönhöfer had postulated that the antimalarial action of mepacrine was connected with the possibility of tautomerism of the following type:



Keeping this in mind, Curd and Rose prepared simple pyrimidines of the general formula (XIII) which are capable of a similar type of tautomerism and which have a molecular weight of the same order as other well known antimalarials.

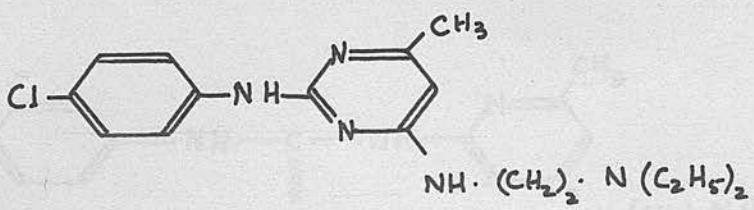


X = p- Cl or m- & p- OCH_3

XIII

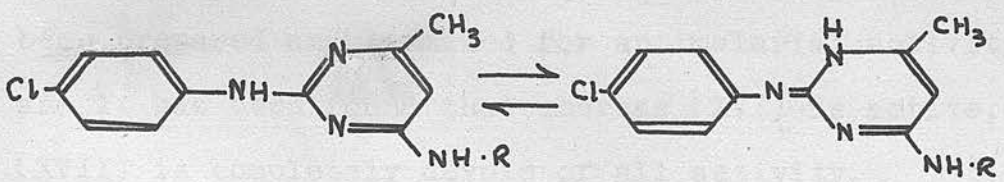
On examination, these compounds were found to be inactive against P. gallinaceum infections in chicks. Activity was produced, however, when

anilino pyrimidines were examined, compound 2666 (XIV) being decidedly active.



(XIV)

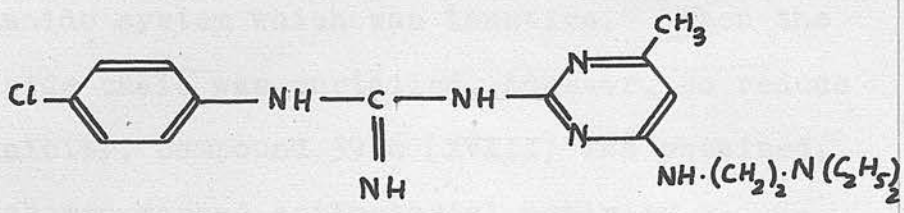
While both these types of compounds involve Schönhöfer's tautomerism, the latter type, exemplified by 2666, is capable of a further kind of tautomerism by virtue of the imino link separating the benzene and pyrimidine nuclei.



$$\left[R = \cdot(CH_2)_2 \cdot N(C_2H_5)_2\right]$$

Thus, besides a basic alkylamino group attached to the pyrimidine nucleus, the presence of an aryl group linked through a grouping capable of

prototropic change appeared necessary for activity. This hypothesis led to compound 3349 (XV), and the introduction of a guanidino linkage which offered similar tautomeric possibilities.

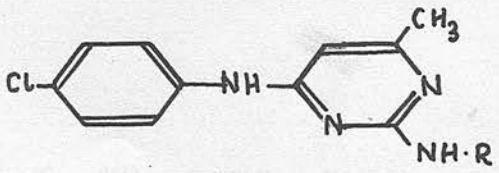


(XV)

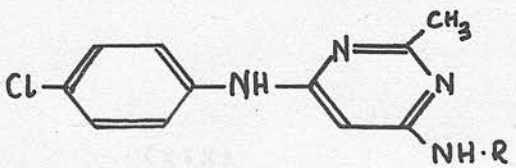
This compound was more active against P. gallinaceum in chicks than the original 2666. It was also shown to possess activity against P. vivax, P. malariae and P. falciparum infections in human malaria.

The isomers (XVI and XVII) of 2666 have also been prepared and examined for antimalarial activity, and it has been found that whereas (XVI) is active, (XVII) is completely devoid of all activity.

(XVI)

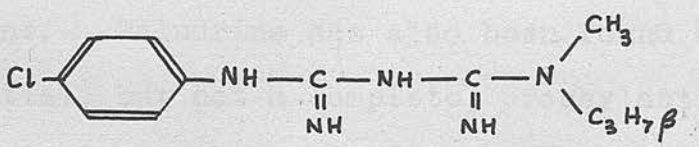


(XVII)



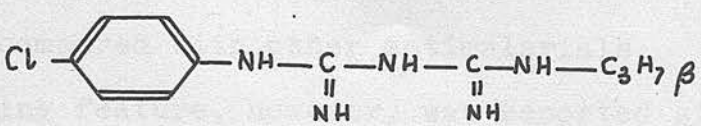
[R = ·(CH2)2·N(C2H5)2]

It therefore appears that activity is associated with two linked but independent amidine systems. Removal of carbon atoms five and six of the pyrimidine ring, a modification which does not affect the conditions for activity discussed above, resulted in a biguanide system which was inactive. When the basic side chain was curtailed, however, to reduce the basicity, compound 3936 (XVIII) was obtained, which showed marked antimalarial activity.



(XVIII)

A further modification yielded paludrine (XIX) — N1-p-chlorophenyl-N_5-isopropyl-biguanide —



(XIX)

Fairley in 1946 carried out an extensive series of prophylactic and therapeutic trials with paludrine on volunteers exposed to New Guinea strains of P. falciparum, and on troops suffering from malaria contracted in this area. In the former case, paludrine was found to act as a true causal prophylactic, and in the latter, radical cure was effected in 100% of cases after a ten days' course of treatment with the drug. Recently, however, Covell (1949) has reported that with West African strains of P. falciparum, radical cure is not effected with paludrine alone. Paludrine has also been found to act as a partial, but not a complete, prophylactic in vivax malaria. A point of great sanitary significance is that although paludrine is not gametocidal, if mosquitoes ingest the blood of paludrine-treated patients infected with gametocytes, sexual development in the insect host is inhibited, so that sporozoites are not formed. This factor is of great value in preventing spread of the disease. Another point in favour of paludrine is its very low toxicity compared with other antimalarials. One disappointing feature, however, was reported simultaneously by Bishop and Birkett, and by Williamson, Bertram and Lourie in 1947. These workers found strains of P. gallinaceum which developed resistance to paludrine

after repeated treatment with the drug. These strains, while also resistant to the methyl homologue of paludrine, N_1-p-chlorophenyl-N_5-methyl-N_5-isopropylbiguanide, were found to be sensitive to quinine, plasmoquine and mepacrine. The development of sporozoites in the gut of mosquitoes fed on patients treated with paludrine and carrying gametocytes of these strains in the blood stream, no longer occurred, and the resistance was found to persist even after five passages through the mosquito without intervening drug treatment. Recently (1948) Bishop and McConnachie obtained a strain of P. gallinaceum in young chicks, with a resistance to sulphadiazine thirty-two times greater than that of the untreated strain. Furthermore this sulphadiazine-resistant strain was found to be resistant to relatively large doses of paludrine, and a paludrine-resistant strain, which had been subjected to prolonged treatment with the drug, was also found to exhibit cross-resistance to sulphadiazine. This point appears to indicate some similarity in the mode of action of the two drugs. Resistance to quinine was unknown until Knoppers (1947) described a twofold increase in resistance in P. gallinaceum in chicks, which was partially lost, however, after one passage through a mosquito. All attempts to

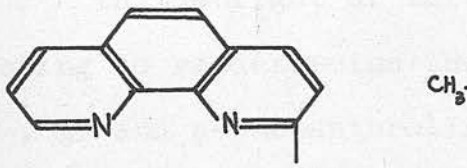
produce strains resistant to mepacrine and pyrimidine derivatives such as 3349 appear so far to have been unsuccessful. This last result, suggesting a different mode of action for paludrine and the pyrimidine compounds, is rather surprising when one considers the close structural relationship between the two compounds.

Many paludrine-like compounds have been prepared and tested for antimalarial activity. Of these, only the 3:4 dichloro-analogue of paludrine has been found to have a higher activity than paludrine itself. It is of great interest that when the chlorine atom is replaced by a methyl group, the resulting compound is inactive.

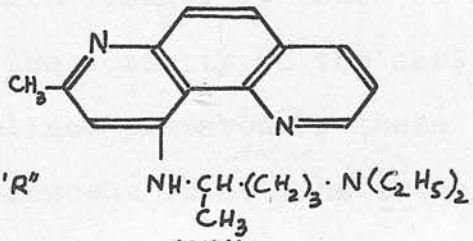
As has been stated previously, following the introduction of plasmoquine and mepacrine, a great deal of work was carried out in attempts to synthesise derivatives of quinoline and acridine, which would equal or surpass the activity of the model compounds. Furthermore, attention was directed towards such heterocyclic ring systems as phenanthridine, pyridoquinolines, benzquinolines, quinazoline, benziminazole and carbazole. In some cases, a definite degree of activity was observed, but until the discovery of paludrine, no drug was evolved which could displace mepacrine clinically, from its

position as the most generally useful synthetic antimalarial.

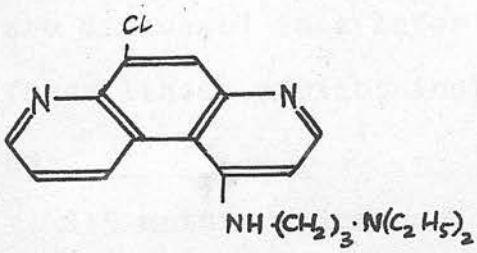
Kermack and co-workers carried out a series of investigations on the o-, m- and p-phenanthrolines, which may be regarded as angular pyrido-quinolines. Halcrow and Kermack (1946) prepared 2-dialkylamino-alkylamino-o-phenanthrolines (XX), but the products were inactive. m-Phenanthrolines carrying basic side chains in positions two and four were synthesised by Kermack and Webster (1942) and Kermack and Tebrich (1945). One of these compounds, 4-(δ-diethylamino-α-methylbutylamino)-2-methyl-m-phenanthroline showed doubtful activity against P. relictum in canaries (XXI). Derivatives of p-phenanthroline have been prepared by Kermack and Weatherhead (1940), Jacomb and Kermack (1946), Douglas, Jacomb and Kermack (1947) and Douglas and Kermack (in the press). The latter workers found that 4-(δ-diethylamino-α-methyl-butylamino)-p-phenanthroline, and 9-chloro-4-(γ-diethylamino-propylamino)-p-phenanthroline (XXII) showed definite activity against P. gallinaceum infections in chicks. Kermack and Weatherhead had previously prepared 4-(δ-diethylamino-propylamino)-p-phenanthroline (XXIII) which was found to be inactive against P. relictum in canaries. It therefore appeared to be of great interest to test the



(XX)



(XXI)



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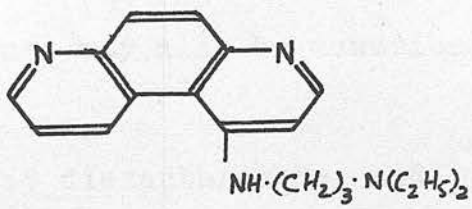

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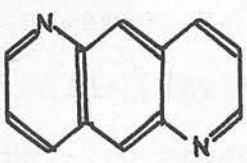

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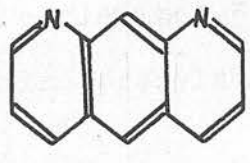


(XXV)

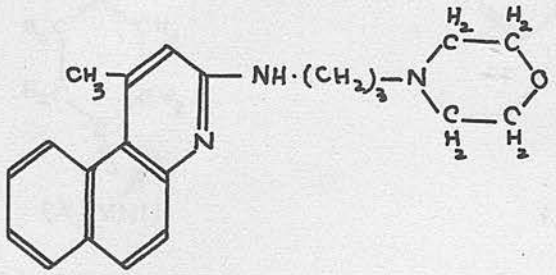
latter compound against P. gallinaceum in chicks. This time, definite antimalarial activity was observed. In the light of this result, it would be interesting to re-determine the activity of the earlier o-, m- and p-phenanthrolines prepared by these workers, against P. gallinaceum infections in chicks.

Since these phenanthrolines represent angular pyridoquinolines, it was considered desirable to prepare the corresponding linear pyridoquinolines. Attempts to prepare derivatives of the isomeric $6:7:2^1:3^1$ (XXIV) and $6:7:3^1:2^1$ (XXV) pyridoquinolines are discussed in a later section of this thesis. These linear pyridoquinolines may also be described as

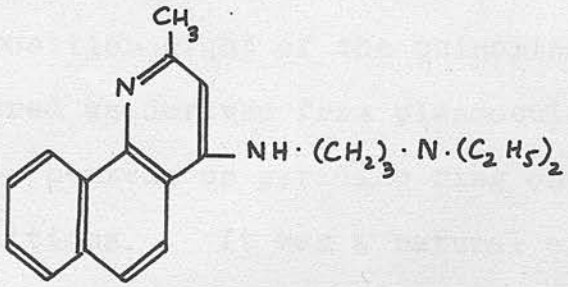
1:5 anthrazoline or 1:5 diazanthracene and

1:8 anthrazoline or 1:8 diazanthracene.

A great many angular 5:6-(f) and 7:8-(h) benzquinolines have been prepared and tested for antimalarial activity. Most of them are inactive or only slightly active. Of those reported in the Survey of Antimalarial Compounds, the most active are 4-methyl-2-(4^1-morpholinylpropylamino)-5:6 benzquinoline (XXVI) and 4-diethylamino propylamino-2-methyl-7:8 benzquinoline (XXVII).

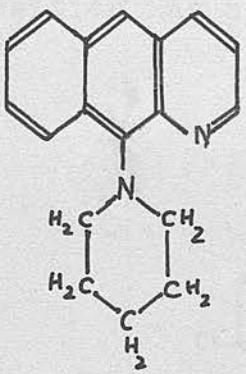


(XXVI)

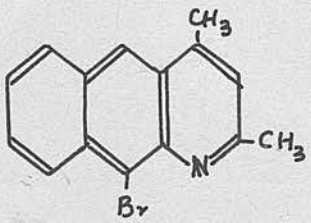


(XXVII)

Only one linear 6:7-(g)-benzquinoline derivative is to be found in the Survey of Antimalarial Compounds — 8-(1^1-piperidyl)-6:7 benzquinoline (XXVIII). This is quite inactive (Q - 0.15). The preparation of 8-bromo-2:4-dimethyl-6:7 benzquinoline (XXIX), which may also be described as 9-bromo-2:4-dimethyl-1-azanthracene, and attempts to replace the bromine atom by a basic side chain and a simple amino group, are discussed later in this thesis.



(XXVIII)

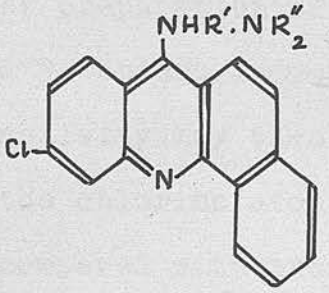


(XXIX)

Benzquinolines and Pyridoquinolines carrying a side-chain in position eight of the quinoline nucleus may be considered as derived from plasmoquine by the fusion of a benzene or pyridine ring on the appropriate positions. It was a natural extension of the work to prepare benzacridines and pyridoacridines related in a similar manner to mepacrine.

Angular 1:2- and 3:4- benzacridines have been prepared by Bachmann and Picha (1946), Dobson and Kermack (1946) and Dobson, Hutchison and Kermack (1948). They found that 8-chloro-5-(dialkylamino-alkylamino)-1:2-benzacridines (XXX) had no anti-malarial activity, Bachmann and Picha's compounds being tested against duck malaria, and those of Kermack and co-workers against P. gallinaceum in chicks. Since 8-chloro-5-(dialkylamino alkylamino)-acridine is active, it is clear that a benzene ring in the

1:2- position has a definite distherapeutic effect.



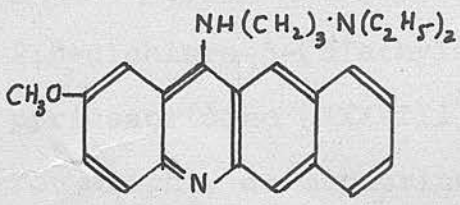
(XXX)

On the other hand, Kermack and co-workers found that 8-chloro-5-(dialkylamino alkylamino)-3:4-benzacridines (XXXI) were decidedly active, the antimalarial activity thus being unimpaired or even enhanced by a benzene ring in the 3:4- position.

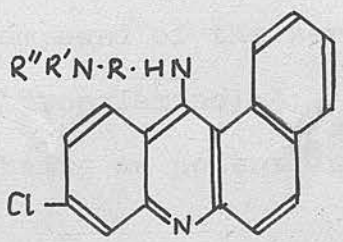
Linear benzacridines have been prepared by Bachmann and Cowen (1948) and Albert, Brown and Duewell (1948). The compounds which Bachmann tested — 7-methoxy-5-(diethylamino-propylamino)-2:3-benzacridine (XXXII) and 5-(6^{1}-methoxy-8^{1}-quinolylamino)-2:3-benzacridine (XXXIII)-were found to be devoid of antimalarial activity. Albert's compounds were simple amino-derivatives, and were tested as antibacterials rather than as antimalarials.

As a chlorine atom in position eight of the acridine nucleus appears to be necessary for activity,

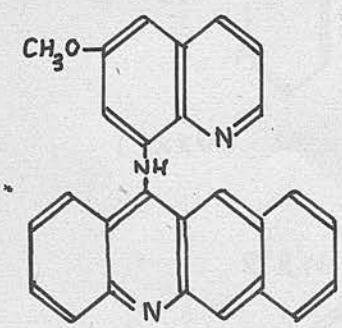
it was of interest to prepare 8-chloro-2:3-benz-acridines (XXXIV) carrying a basic side chain in position five. Part of the work of this thesis is concerned with the preparation of this compound and of the 6-, 7- and 9- chloro isomers which are also of interest, as activity may then be correlated with the position of the chlorine atom in the nucleus, and the results compared with those obtained with the corresponding chloro-acridines.



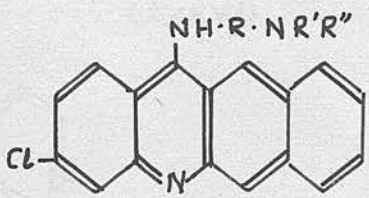
(XXXII)



(XXXI)

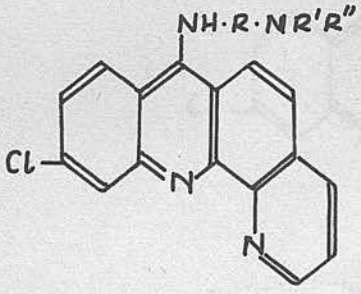


(XXXIII)

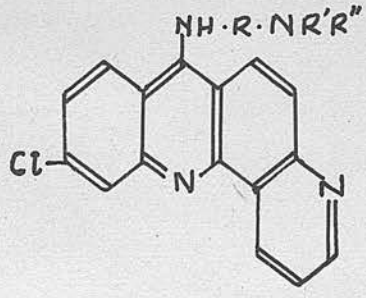


(XXXIV)

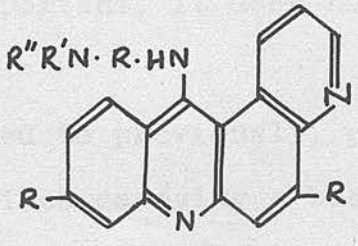
Corresponding to the 1:2- and 3:4- benzacridines, Dobson, Hutchison and Kermack (1948) also prepared angular pyridoacridine derivatives. 8-chloro-5-(dialkylamino-alkylamino)-1:2:2^1:3^1- and 1:2:3^1:2^1-pyridoacridines (XXXV and XXXVI) were found to be completely inactive, while 5-(dialkylamino alkylamino)-3:4:2^1:3^1-pyridoacridines (XXXVII), without the chlorine which seems to be so essential in the simple acridine series, showed a decided, though weak, activity. The activity was greatly increased when chlorine atoms were introduced into the two and eight positions, the most active compound of the series — 2:8-dichloro-5-(diethylamino propylamino)-3:4:2^1:3^1-pyridoacridine (XXXVIII) — being as potent, weight for weight, as mepacrine.



(XXXV)



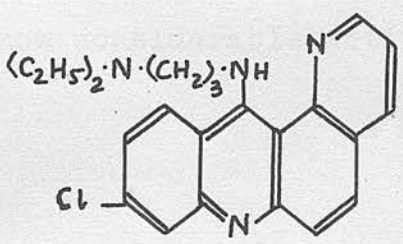
(XXXVI)



(XXXVII) & (XXXVIII)

[R = H] [R = Cl]

The nature of the side chain attached to the nucleus appeared to exert a very slight, though appreciable, influence on the activity of the compound. In the mono-chloro series, the least active compound is that carrying the (diethylaminoethylamino)-side chain, and the most highly active that carrying the (δ-diethylamino-α-methylbutylamino)-grouping. In view of the fact that derivatives of both 3:4-benzacridine and 3:4:2^1:3^1-pyridoacridine are active, it is surprising that 8-chloro-5-(diethylaminopropylamino)-3:4:3^1:2^1-pyridoacridine (XXXIX) is devoid of activity.

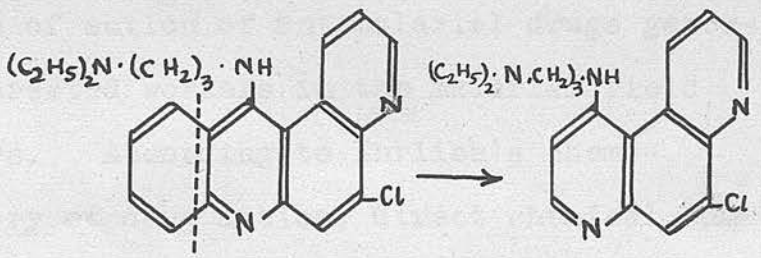


(XXXIX)

Thus while the geometric pattern of the nucleus appears to be important, it does not alone condition activity.

As referred to previously, pyridoquinolines and benzquinolines carrying a basic side chain in position eight may be considered as derived from

plasmoquine. Similarly, the active acridines, benzacridines and pyridoacridines may be regarded as derivatives of chloroquine. The activity of these compounds is considerably less than chloroquine itself, and as they are derived from chloroquine by the addition of one benzene ring, two benzene rings, or a benzene and a pyridine ring, the removal of any of these rings leaving the chloroquine system intact might be expected to enhance, rather than impair, the antimalarial activity of the compound. By this reasoning, 9-chloro-4-(diethylaminopropylamino)-p-phenanthroline (XL), which may be derived from 2-chloro-5-(diethylaminopropylamino)-3:4:2^1:3^1-pyridoacridine (XLI) by removal of a benzene ring, should show considerable activity.



(XLI) (XL)

As already mentioned, this compound has been prepared by Douglas and Kermack, and has been found to

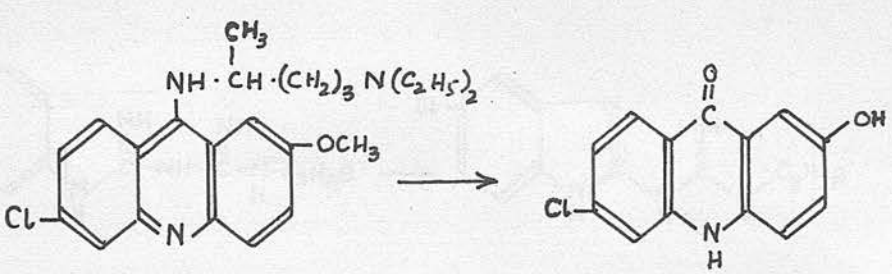
possess activity comparable with that of the original pyridoacridine.

Other compounds which have been tested for antimalarial activity are certain sulphonamides. Of these, sulphadiazine and proseptazine-(N_4-benzylsulphanilamide) are causal prophylactics against P. gallinaceum infections in chicks. The antimalarial activity of sulphadiazine is antagonised by the simultaneous administration of p-aminobenzoic acid, indicating a probable mode of action for sulphadiazine in malaria, similar to that of sulphonamides generally in bacterial infections. However, certain other sulphonamides which are active against malaria, e.g. 2-metanilamido-5-chloro-pyrimidine, are not antagonized by p-aminobenzoic acid, and so, presumably, attack the infection by a route different from that used by sulphadiazine.

The mode of action of antimalarial drugs generally has interested workers in the malarial field for many years. According to Ehrlich's chemoreceptor theory of drug action, direct chemical combination took place between the drug and the parasite. Other theories have been advanced postulating an immunological basis for the action of the drug. It has also been suggested that antimalarials might have some special action on the surface of the

red blood cells, which would prevent the parasite from entering the cell to complete the shizogenous stage of its life cycle. Magidson and co-workers (1934) suggested that in the case of drugs of the acridine and quinoline types carrying long basic side chains, the drug might be considered as composed of two parts, each having separate functions. The basic side chain, termed the conductophoric part of the molecule, they postulated as being concerned with the penetration of the drug into the parasites. The heterocyclic nucleus, or parasiticidal part, would then act as a general protoplasmic poison.

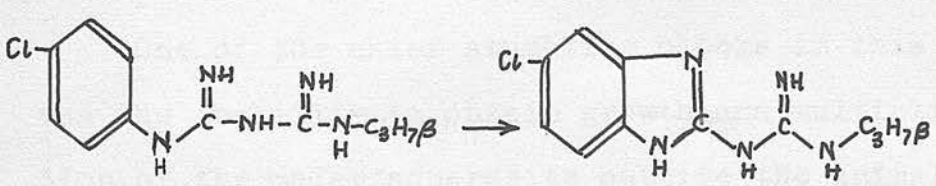
In the case of mepacrine, Magidson and Grigorowsky (1936) suggested that the parasiticide might be 3-hydroxy-8-chloroacridone (XLII), the basic side chain being split off in vivo by enzymic hydrolysis, accompanied by demethylation



(XLII)

This theory is not improbable as when mepacrine is heated with water, a certain amount of 3-hydroxy-8- mellosy

chloroacridone may be isolated. In this connection, some recent work on paludrine is of interest. Tonkin (1946) and Hawking (1947) on investigating the action of paludrine in vitro on P. cynomolgi of monkeys and on the exo-erythrocytic forms of P. gallinaceum grown in tissue culture, found that paludrine was without action on the plasmodia, no inhibition in the development of the parasites being observed. They suggested, therefore, that paludrine itself had no antimalarial properties, but that it is converted in vivo into some active principle. Acheson, King and Spensley (1947) conjectured that the transformation product might be the guanidinobenziminazole (XLIII), which could be formed from paludrine by oxidative ring-closure.



(XLIII)

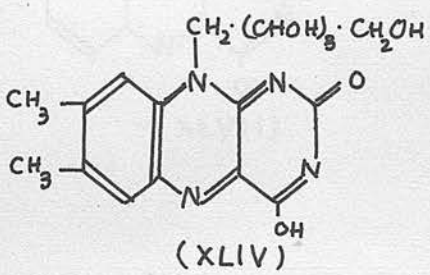
King and co-workers, however, on preparing this guanidinobenziminazole and several analogous compounds,

found they were without action on P. gallinaceum infections in chicks at the maximum tolerated doses. The active product formed from paludrine in vivo does not so far seem to have been identified.

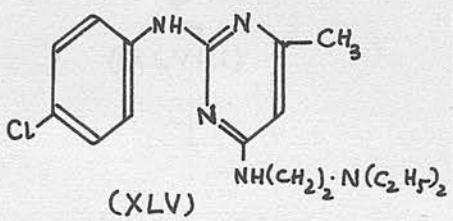
Much of the more recent work on the mode of action of antimalarials has been based on biochemical considerations. It was being realised, more and more, that the current empirical methods, while occasionally producing drugs of considerable practical value, could never elucidate the mode of action of the drug and so lead, in a logical manner, to better antimalarial agents. In the last ten years, therefore, a host of data has been published on the metabolic processes of the malaria parasite, and the effect of antimalarials on such processes. So far, no general theory of antimalarial action has been evolved, but as the available data increases and technique improves, the solution of the problem moves considerably nearer.

One of the chief stumbling blocks in this work was the inability to obtain growth and multiplication of the malaria parasite outside the animal host, but this has been partially overcome by workers such as Ball (1946) and Hawkings (1946). Some of the earliest biochemical work dealt with riboflavin antagonism. Silvermann and Evans (1943) observed

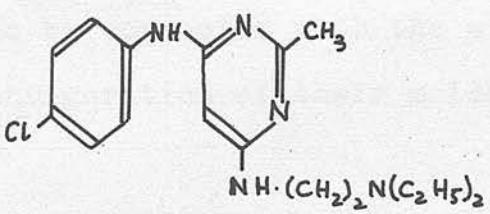
that when tested on L. Casei mepacrine inhibited the growth promoting action of riboflavin (XLIV). As the two compounds have a general structural resemblance, it was suggested that they might compete with each other for some enzyme system essential to the malaria parasite. Evidence in support of this suggestion came from Medinaveitia (1947), who showed that riboflavin antagonises the growth inhibitory action for L. Casei of 2-p-chloroanilino-4 (β -diethylamino-ethylamino)-6-methylpyrimidine (XLV)



(XLIV)

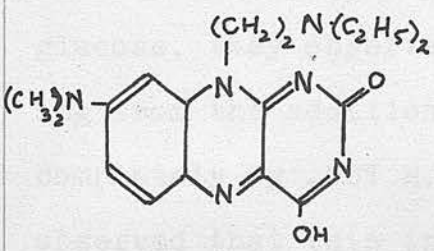


(XLV)

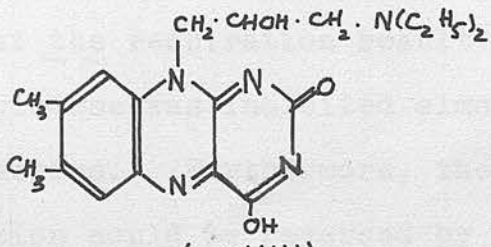


(XLVI)

which also has a certain structural resemblance to riboflavin. However, 4-p-chloroanilino-6-(β -diethylamino ethylamino)-2-methyl pyrimidine (XLVI) which resembles riboflavin rather more closely, and which was already known to possess no antimalarial activity, was completely inactive in its power to antagonise riboflavin. King (1948) and Mosher (1946) have synthesised compounds containing the alloxazine nucleus, (XLVII and XLVIII), e.g.



(XLVII)



(XLVIII)

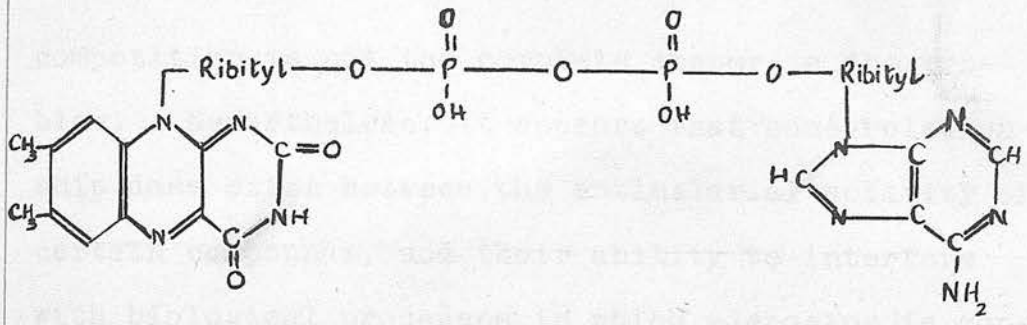
but found no reversal of the growth promoting activity of riboflavin and no trace of antimalarial activity. Thus the activity of antimalarial drugs does not appear to be connected with the similarity in the spatial configuration of their molecules to riboflavin.

Speck and Evans (1945), working on the carbohydrate metabolism of the malaria parasite, found

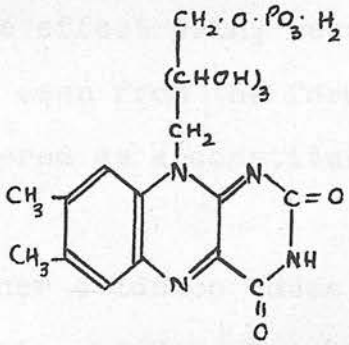
evidence indicating that the utilization of glucose involved the same reactions and the same phosphorylated intermediates as are found in yeast and muscle. Now the first step in the utilization of glucose is the formation of glucose-6-phosphate, adenosine triphosphate functioning as a carrier of energy-rich phosphate bonds, and the enzyme, hexokinase, as catalyst. Speck and Evans have shown that mepacrine inhibits hexokinase very strongly, and recently Hellerman and Bovarnick (1946) have demonstrated competition between mepacrine and adenosine triphosphate. Thus, with parasites initially depleted of glucose, they observed that the respiration resulting from the addition of glucose was inhibited almost completely by .001 M. mepacrine. Furthermore, they observed that this inhibition could be reversed by adenylic acid or adenosine triphosphate. Quinine and plasmoquine were found to have similar effects, so that antimalarials appear to interfere radically with the carbohydrate metabolism of the parasite. Hellerman and co-workers also demonstrated that mepacrine and quinine were general enzyme poisons. The enzymes d-amino-acid oxidase, diaphorase, lactic dehydrogenase, pancreatic lipase and catalase are all inhibited by mepacrine, plasmoquine and quinine. However, these workers also observed that many non-

antimalarial quinolines exerted a similar inhibitory effect on these enzymes, so that no definite conclusions could be drawn from these studies. A great deal of general information of this kind is available, some of which has been summarised in the account given of a Symposium on the Malaria Parasite in Federation Proceedings (1946).

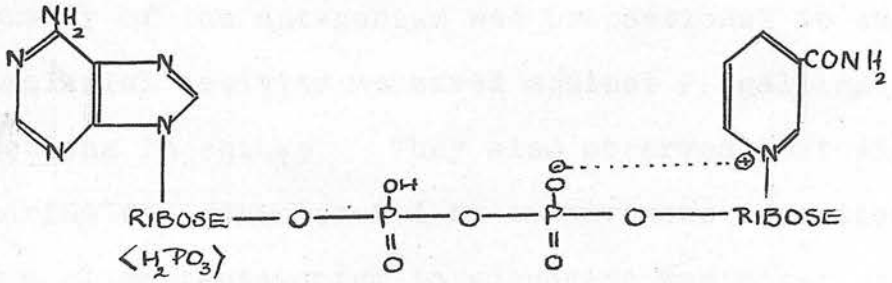
As already described, the structural similarity between riboflavin and mepacrine, and the existence of antagonism between these compounds in certain instances, suggested a theory of competition between riboflavin and antimalarial drugs which was not upheld by later work. However, Haas (1944), and Wright and Sabine (1944), have shown that the flavin enzymes, diaphorase and d-amino-acid oxidase (XLIX) are inhibited by mepacrine. The prosthetic groups of both these enzymes are dinucleotides which may be considered as built up from riboflavin and adenosine along with phosphate groups. As competition exists between adenosine and mepacrine, the apparent antagonism observed between riboflavin and certain antimalarials may be due, not to riboflavin itself, but to a flavin enzyme containing adenosine. However, Haas has also shown that cytochrome reductase (L), which contains only riboflavin in its prosthetic group, is inhibited by mepacrine, so adenosine


Ribityl
O
P
OH
Ribityl
CH3
CH3
C=O
NH
NH2

(XLIX)


CH2·O·PO3·H2
(CHOH)3
CH2
CH3
CH3
C=O
NH

(L)


NH2
CONH2
RIBOSE
RIBOSE
OH

(LI)

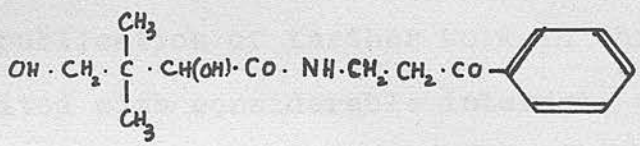
competition is not the complete answer to the problem. Nevertheless, it appears that some relationship does exist between the antimalarial activity of certain compounds, and their ability to interfere with biological processes in which adenosine is concerned.

Thus, glucose-6-phosphate dehydrogenase which catalyses the aerobic oxidation of glucose-6-phosphate to phosphogluconic acid, is inhibited by mepacrine, the effect being reversed by co-enzyme II (LI). As may be seen from the formula, adenosine may also be considered as a constituent of this co-enzyme molecule.

Further evidence comes from some work by Medinavietia and Raventos (1949). These workers measured the duration of the auriculo-ventricular block produced by intravenous and oral administration of adenosine to guinea pigs, and the effect of antimalarial drugs on this duration. They found that antimalarials antagonised adenosine and that, with the exception of the anilino-pyrimidines, the intensity of the antagonism was proportional to the antimalarial activity measured against P. gallinaceum infections in chicks. They also observed that when paludrine was administered by intravenous injection, only a slight antagonism to adenosine was observed

with quite high concentrations, while, when given orally, the reverse effect was observed. This supports the Hawking's theory that paludrine itself has no antimalarial activity, but is transformed in vivo into some active metabolite.

The discovery of the antimalarial activity of pantothenophenone is noteworthy, as it developed logically from some work by Trager (1943), who found evidence that pantothenic acid { } was a growth factor of P. lophurae. Analogues of pantothenic acid were accordingly prepared and tested against P. gallinaceum infection in chicks, the most active, pantothenophenone (LII) (Woolley, 1947), when given orally, being as effective as quinine.



(LII)

In conclusion, attention might be drawn to some very interesting observations of Laser and Friedman (1945). These workers isolated a haemolytic substance from normal blood. Later (1946), they reported that the rate of haemolysis produced by this

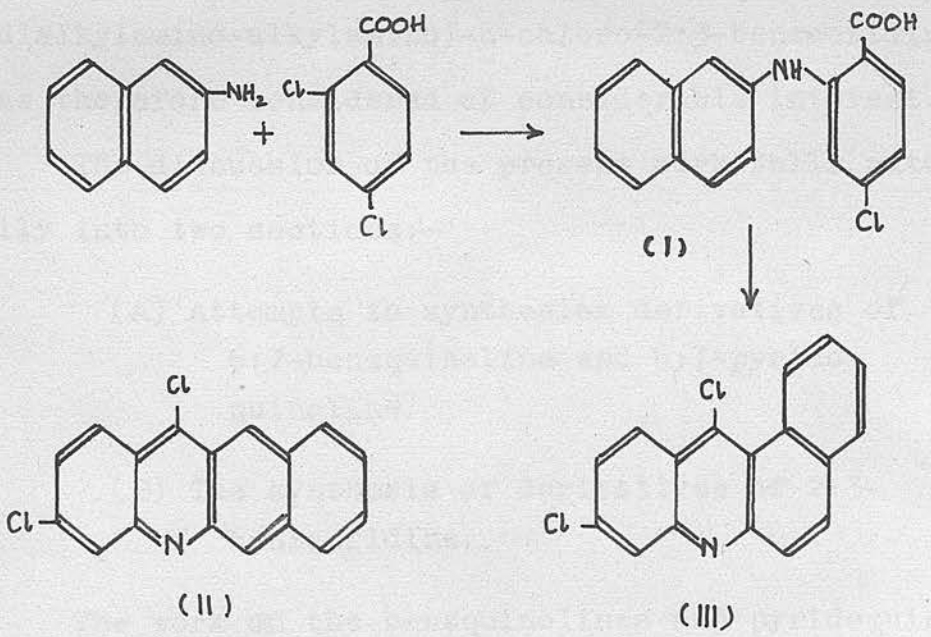
substance in vivo, was decreased by the addition of antimalarial drugs. No decrease was observed with substances devoid of antimalarial activity. Laser and Friedman suggested that the malaria parasite might produce a metabolite, closely related to the naturally occurring haemolytic substance, and that antimalarial drugs acted by inhibiting the haemolytic action of this metabolite. In a later publication (1948), Laser reported that the haemolytic substance from normal blood had been isolated and was probably an unsaturated monocarboxylic fatty acid having one double bond and a possible chain length C 18. The content of haemolytic substance isolated from heavily parasitized blood of monkeys infected with P. knowlesi was twenty-five to seventy-five times that in normal blood, and was indistinguishable from the normal haemolytic factor.

The publication of further work in this line is being awaited with considerable interest.

II. GENERAL DISCUSSION.

As indicated in the introduction to this thesis, most of the present research is concerned with preparation of linear 6:7-benzquinolines, 6:7-pyridoquinolines and 2:3-benzacridines. A great deal of work has been published on the angular analogues of these compounds, but very little appears to have been done on the linear ring systems. This may be due to the fact that most of the usual methods for the addition of pyridine rings to an aromatic system, for example, those of Skraup, Döbner-Miller and Conrad-Limpach, result in the formation, not of linear, but of angular ring compounds. A striking exception to the general rule is Combes' method, developed by Johnson and Mathews (1944). Here the condensation of an aromatic amine with acetyl acetone, and the cyclization of the resulting anil by dropping it into chilled concentrated sulphuric acid, results mainly in the formation of a linear ring system. Johnson and Mathews found that conditions for linear ring-closure were even more favourable if anhydrous hydrogen fluoride were used as the cyclizing agent. Combes' method has been employed with successful results during the course of the present research on the synthesis of linear 6:7-benzquinoline derivatives.

It has already been mentioned in the introduction to this thesis that Kermack and co-workers prepared angular benzacridine and pyridoacridine derivatives. The general method they used was to condense a suitable amine with a derivative of o-chlorobenzoic acid, and to ring-close the product with phosphorous oxychloride. In some cases, for example when β-naphthylamine is condensed with 2:4-dichlorobenzoic acid to yield 4-chloro-2-(β-naphthylamino)-benzoic acid (I), ring-closure with phosphorus oxychloride could take place in two positions to form either the linear 5:8-dichloro-2:3-benzacridine (II), or the angular 5:8-dichloro-3:4-benzacridine (III).



As the a-priori likelihood of the angular compound being formed in such cases was very great, Kermack et al assumed that the product obtained was 5:8-dichloro-3:4-benzacridine. One of the objects of this research was to prepare 5:8-dichloro-2:3-benzacridine by an unambiguous route, so that angular cyclization in the former case could be definitely established. This latter compound is also of particular interest as, by replacing the chlorine atom in position five of the nucleus by a basic side-chain, a mepacrine-like compound is formed having the chlorine atom in position eight, a feature of mepacrine which appears to be intimately connected with its antimalarial activity. Bachmann (1948) has prepared similar linear benzacridine derivatives, but without a chlorine atom in this position. The preparation of 5-(dialkylamino-alkylamino)-8-chloro-2:3-benzacridine was therefore considered of considerable interest.

The discussion of the present work falls naturally into two sections:-

(A) Attempts to synthesise derivatives of 6:7-benzquinoline and 6:7-pyridoquinoline.

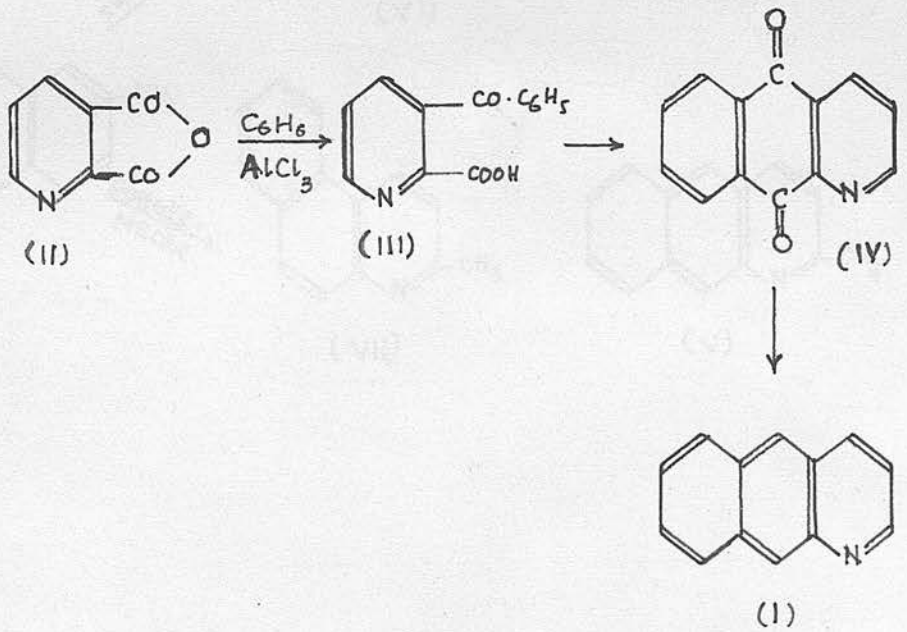
(B) The synthesis of derivatives of 2:3-benzacridine.

The work on the benzquinolines and pyridoquino-

lines has been grouped together, as the synthetic methods used in both cases were very similar, and it has been found convenient to discuss the results collectively.

(A) ATTEMPTS TO SYNTHESISE DERIVATIVES OF 6:7-BENZQUINOLINE AND OF 6:7-PYRIDOQUINOLINE.

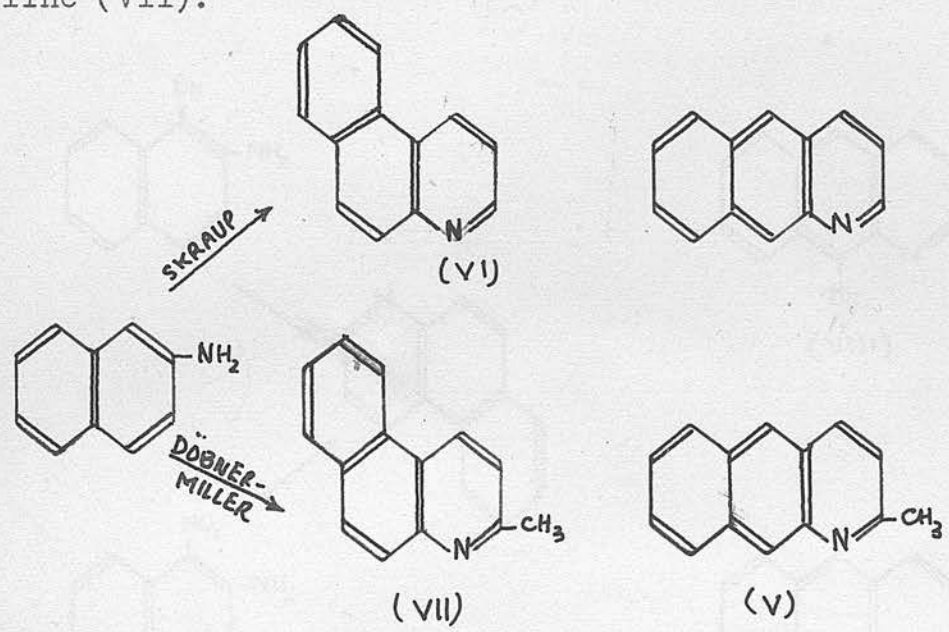
6:7-benzquinoline (I), described in the early literature as anthrapyridine, and in more modern times as 1-azanthracene, was first prepared by Jahren and Phillips (1894). These workers converted the anhydride of quinolinic acid (II) to benzolypicolinic acid (III) by reaction with benzene and aluminium chloride, cyclized the latter acid with sulphuric acid, and reduced the resulting 1-azanthraquinone (IV) with zinc dust and ammonia.



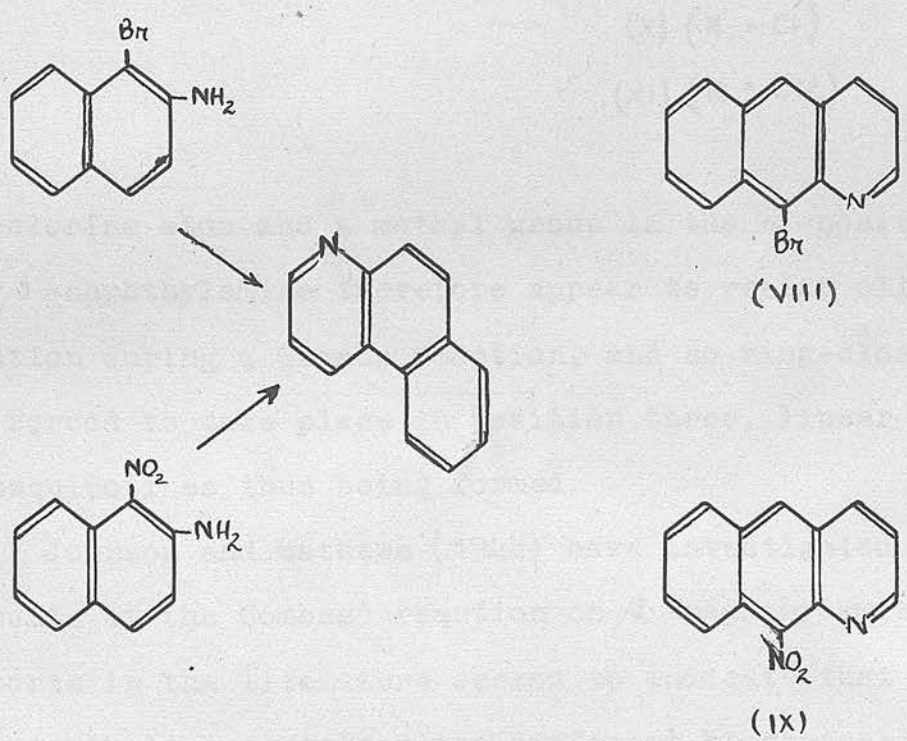
(II) (III) (IV)

(I)

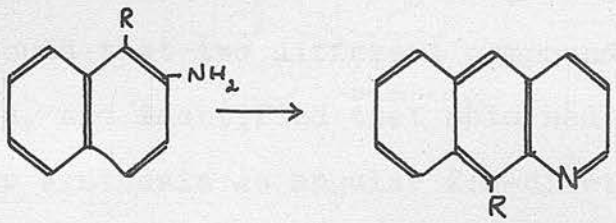
Previously, Döbner and Miller (1884) and Lellman and Schmidt (1884) had attempted to prepare 6:7-benzquinoline (I) and its 2-methyl derivative (V) by carrying out a Skraup reaction and a Döbner-Miller synthesis on β-naphthylamine. In both reactions, cyclization may theoretically take place in either the one or three position of the naphthalene nucleus. It was found, however, that neither of the possible linear isomers were formed, but that cyclization had taken place completely in the one position to form 5:6-benzquinoline (VI) and 2-methyl-5:6-benzquinoline (VII).



It therefore appeared that the angular isomer was being formed in preference to the linear compound. The strength of the preference for the angular type of ring-closure was demonstrated when Skraup reactions were carried out on 1-bromo- and 1-nitro-β-naphthylamine. In both cases, in place of the expected 8-bromo- (VIII) and 8-nitro-6:7-benzquinolines (IX), angular 5:6-benzquinoline was again obtained, the bromine atom and the nitro-group being completely eliminated. This result will be discussed later in this section.



However, Gerhardt and Hamilton (1944) and Étienne (1944) obtained 8-chloro-6:7-benzquinoline (X) by a Skraup reaction on 1-chloro-β-naphthylamine, though in poor yield. Marckwald (1893) also found that 8-methyl-6:7-benzquinoline (XI) was formed by a Skraup reaction on 1-methyl-β-naphthylamine.



(X) (R = Cl)

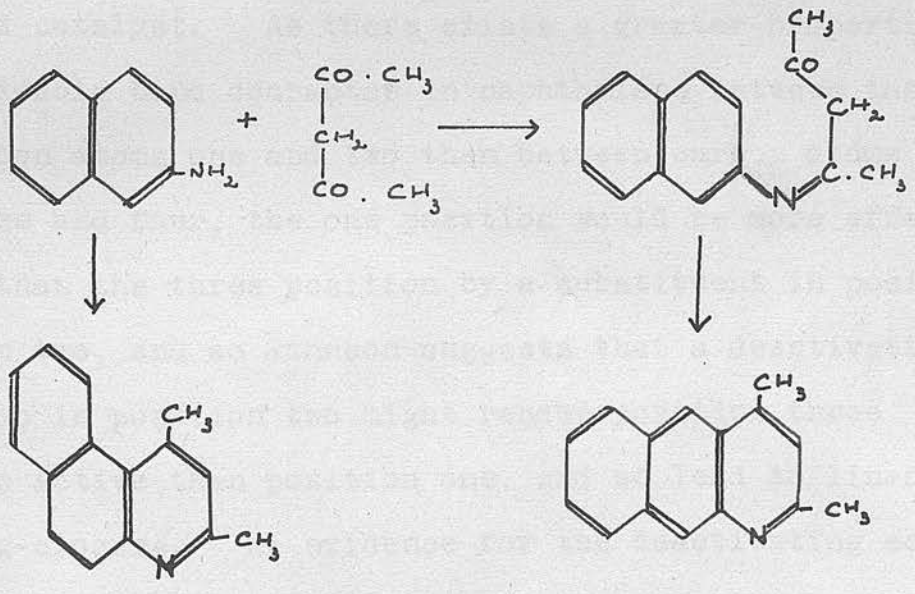
(XI) (R = CH_3)

A chlorine atom and a methyl group in the α-position of β-naphthylamine therefore appear to resist elimination during a Skraup reaction, and so ring-closure is forced to take place in position three, linear benzquinolines thus being formed.

Johnson and Mathews (1944) have investigated the results of the Combes' reaction on β-naphthylamine. Reports in the literature seemed to indicate that β-naphthylamine yielded two different benzquinoline derivatives, one, m.p. 126-7°, obtained by a Döbner-Miller synthesis using paraldehyde and acetone (Reed,

1887), and the other, m.p. 66-7°, obtained by a Combes' synthesis (Combes, 1888) using acetyl acetone. Both these compounds gave a molecular formula of $C_{15}H_{13}N$, and, as angular ring-closure was considered at that time to be the normal result in the synthesis of quinoline derivatives, it was thought that some discrepancy existed in the results of these experiments.

Johnson and Mathews, on reinvestigating these reactions, found that two different compounds were indeed formed, and identified that obtained by the Döbner-Miller synthesis as angular 2:4-dimethyl-5:6-benzquinoline (XII), and that obtained by the Combes' synthesis as linear 2:4-dimethyl-6:7-benzquinoline (XIII).

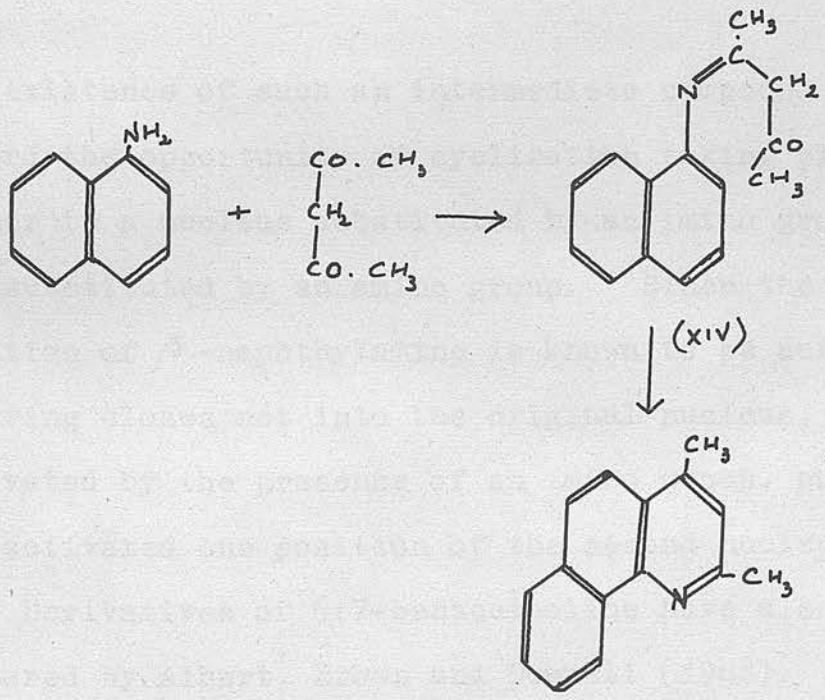


(XII) (XIII)

They also reported that if certain conditions were strictly adhered to, the linear isomer could be obtained in 80% yield by the Combes' synthesis, and furthermore, that if anhydrous hydrogen fluoride were used as cyclizing agent, ring-closure to the linear compound was effected in 96% yield.

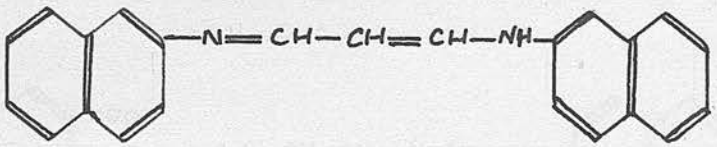
The explanation for the remarkable difference between the result of the Combes Reaction and those of the Skraup, Döbner-Miller, Conrad-Limpach, etc., is not quite clear. Johnson, Woroch and Mathews (1947) have suggested that the abnormal preference in the former case, for cyclization into the three rather than into the one position of the naphthalene nucleus, may be due to the deactivating effect of the side chain in position two, under the influence of the acid catalyst. As there exists a greater proportion of double bond character in naphthalene between the carbon atoms one and two than between carbon atoms three and four, the one position would be more affected than the three position by a substituent in position two, and so Johnson suggests that a deactivating group in position two might render position three more active than position one, and so lead to linear ring-closure. As evidence for the deactivating action of this side chain, he points out that whereas the product obtained from the condensation of

β-naphthylamine and acetyl acetone is cyclized by hydrogen fluoride at room temperature with quantitative yield, that obtained from α-naphthylamine and acetyl acetone (XIV) is not cyclized under these conditions, and requires much more drastic treatment to form 2:4-dimethyl-7:8-benzquinoline (XV), even though, in both cases, cyclization takes place into a β-position of the naphthalene nucleus. The difference in the two cases appears to be in the proportion of double bond character between the position of attachment of the side chain and the position into which the ring closes.



(XV)

Johnson et al also refer to a suggestion by Sidgwig (1942) that the angular cyclization obtained by the Skraup reaction on β-naphthylamine might be attributed to the formation of an anilino anil (XVI).

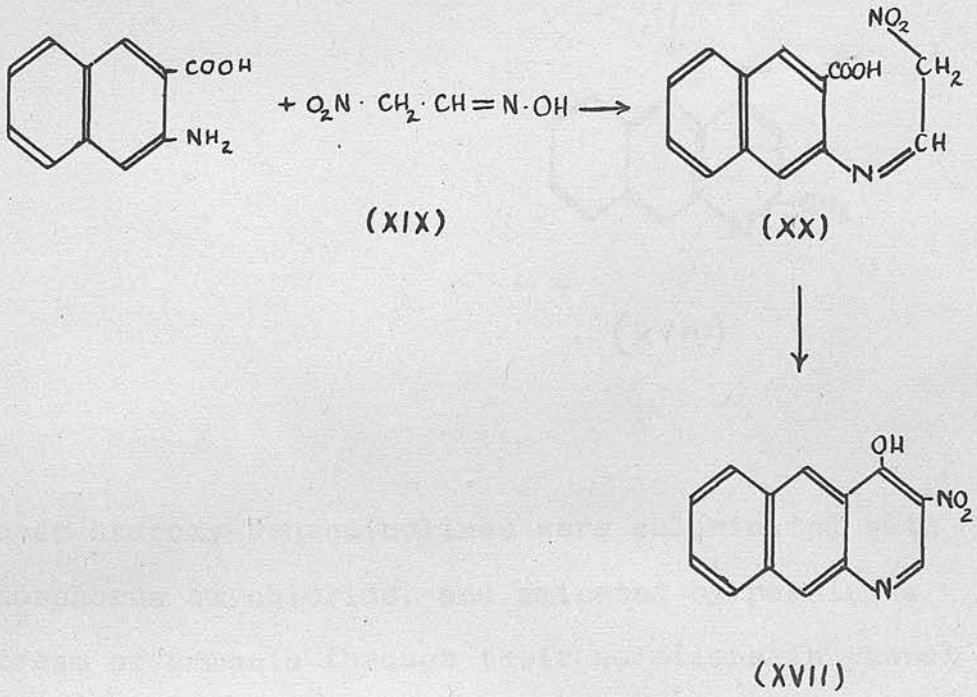


(XVI)

The existence of such an intermediate compound would afford the opportunity of cyclization taking place either in a nucleus substituted by an imino group or one substituted by an amino group. Since the α-position of β-naphthylamine is known to be active, the ring closes not into the original nucleus, deactivated by the presence of an imino group, but into the activated one position of the second nucleus.

Derivatives of 6:7-benzquinoline have also been prepared by Albert, Brown and Duewell (1948). After stressing the difficulties usually found in the preparation of linear compounds of this type, they

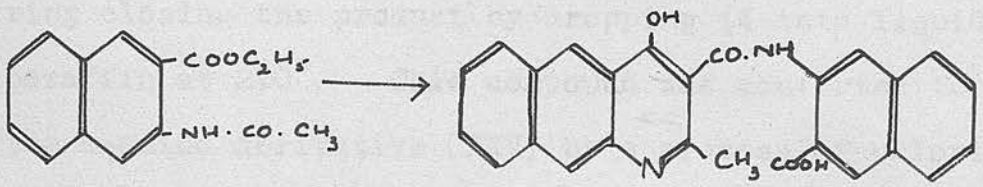
describe the preparation of 3-nitro-4-hydroxy- (XVII) and 4-hydroxy-2-methyl-6:7-benzquinoline (XVIII). They prepared the nitro derivative by condensing 3-amino-2-naphthoic acid with sodium methazonate (XIX) and ring-closing the resulting 3-(β-nitroethylidin-amino)-2-naphthoic acid (XX) with acetic anhydride.



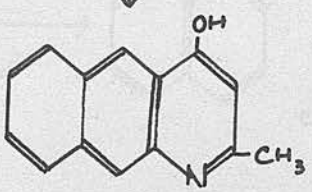
(XIX) (XX) (XVII)

4-hydroxy-2-methyl-6:7-benzquinoline (XVIII) was obtained by acetylating ethyl-3-amino-2-naphthoate, treating this ester with phosphorus oxychloride to yield 4-hydroxy-2-methyl-6:7-benzquinoline-3-carboxy-(2^1-carboxy-3^1-naphthyl) amide (XXI), and subjecting

this compound to simultaneous hydrolysis and decarboxylation by treatment with sulphuric acid.

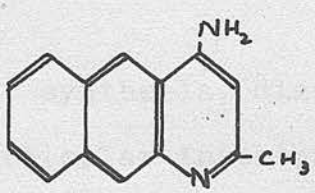


(XXI)

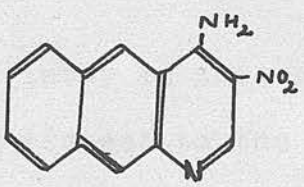


(XVIII)

These hydroxy-benzquinolines were chlorinated with phosphorus oxychloride, and aminated by passing a stream of ammonia through their solutions in phenol at 180°, the products being 4-amino-2-methyl- (XXII) and 3-nitro-4-amino-6:7-benzquinoline (XXIII).

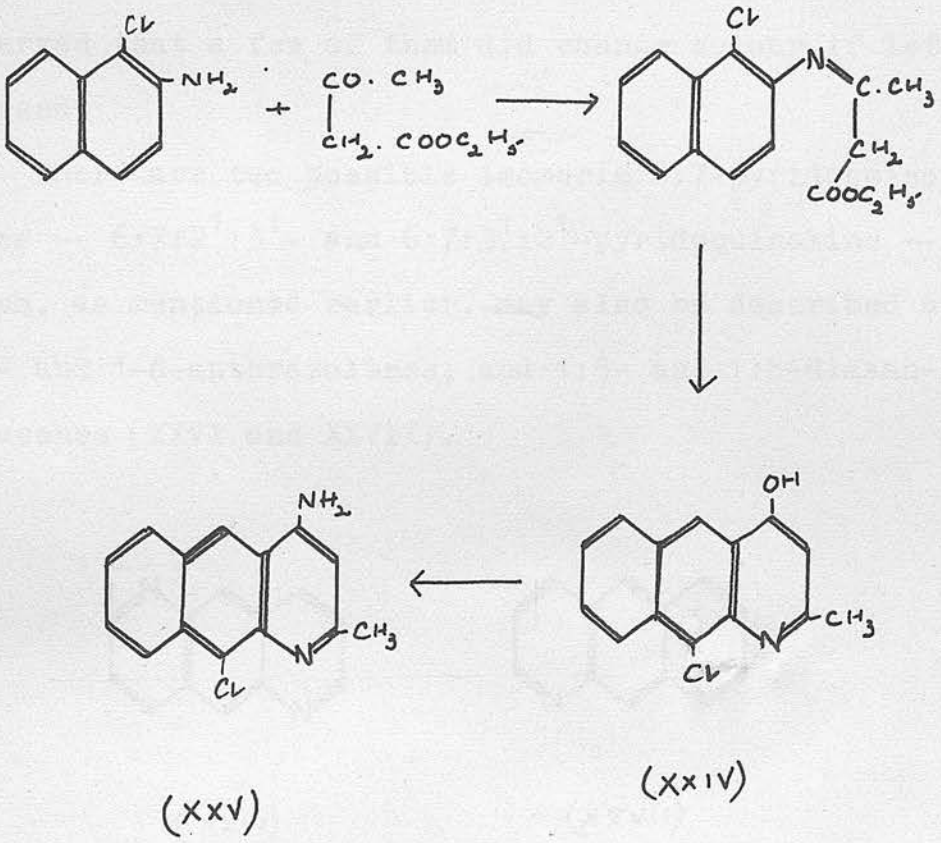


(XXII)



(XXIII)

Albert et al also prepared 8-chloro-4-hydroxy-2-methyl-6:7-benzquinoline (XXIV) by condensing 1-chloro-β-naphthylamine with ethylacetoacetate and ring closing the product by dropping it into liquid paraffin at 270°. This compound was converted to the 4-amino derivative (XXV) by a process of chlorination and amination similar to that described above.

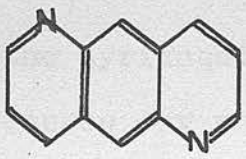


(XXV) (XXIV)

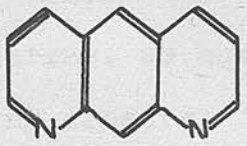
This last synthesis, discussed later in this section, is of particular interest with respect to the present research.

The photochemistry of some linear benzquinolines has recently been studied by Étienne (1946). He found that 6:7-benzquinoline and its 8-chloro derivative were converted to quinones in strong sunlight, and that the latter compound also formed a dimer. During the present research, suitable precautions have been taken to shield all linear benzquinolines and pyridoquinolines from bright sunlight, as it was observed that a few of them did change colour if left exposed.

There are two possible isomeric 6:7-pyridoquinolines — 6:7:2^1:3^1- and 6:7:3^1:2^1-pyridoquinoline — which, as mentioned earlier, may also be described as 1:5- and 1-8-anthrazolines, and 1:5- and 1:8-diazanthracenes (XXVI and XXVII).



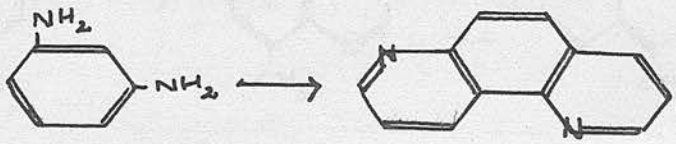
(XXVI)



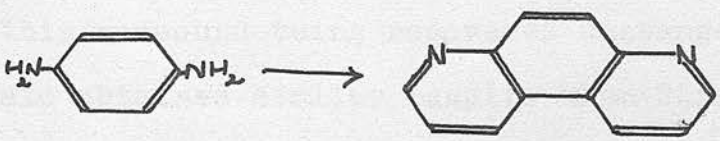
(XXVII)

Theoretically, these compounds ought to be formed by Skraup reactions on m- and p-phenylenediamine. In practice, however, such experiments have been found to yield only the isomeric angular m- and p-phenan-

throlines (XXVIII and XXIX), no linear products being formed.

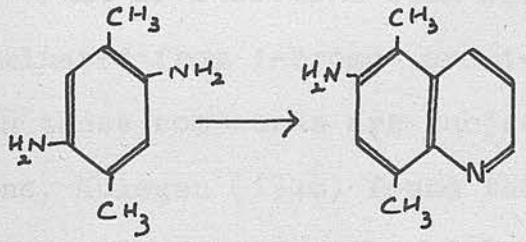


(XXVIII)



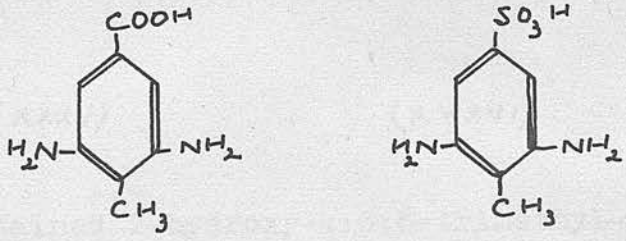
(XXIX)

Thus, in the pyridoquinoline series, we again find this preference for angular ring closure. Marckwald (1894) in an attempt to prevent the formation of angular compounds, carried out a Skraup reaction on p-xylylenediamine (XXX), thus blocking the one and four positions of the benzene ring with methyl groups. Only 5:8-dimethyl-6-aminoquinoline (XXXI) could be isolated from the reaction mixture, however, no trace of any 5:8-dimethyl-6:7:2^1:3^1-pyridoquinoline (XXXII) being found.



(XXX) (XXXI) (XXXII)

Furthermore, no reaction took place when a second Skraup was carried out on 5:8-dimethyl-6-aminoquinoline, this compound being recovered unchanged. Marckwald obtained similar results when Skraup reactions were carried out on 3:5-diamino-4-methylbenzoic acid (XXXIII), and 3:5-diamino-4-methylbenzenesulphonic acid (XXXIV)

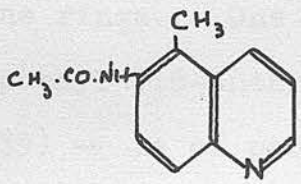


(XXXIII) (XXXIV)

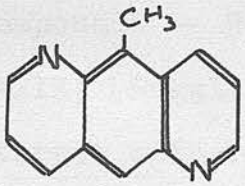
The formation of these linear systems by this method

thus appears to be a matter of considerable difficulty.

Just as a bromine atom and a nitro group are eliminated from 1-bromo- and 1-nitro-β-naphthylamine when these compounds are subjected to Skraup reactions, Huisgen (1948) found that when Skraup reactions were carried out on 5-bromo- and 5-nitro-6-aminoquinoline, no linear products were obtained, but p-phenanthroline was isolated in 65% yield. However, a methyl group appears to resist elimination as, on carrying out a Skraup on 5-methyl-6-acetamidoquinoline (XXXV), Huisgen was able to identify 10-methyl-6:7:2^1:3^1-pyridoquinoline (XXXVI) as one of the products of the reaction.

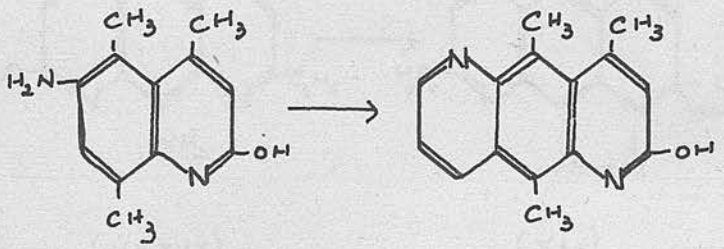


(XXXV)



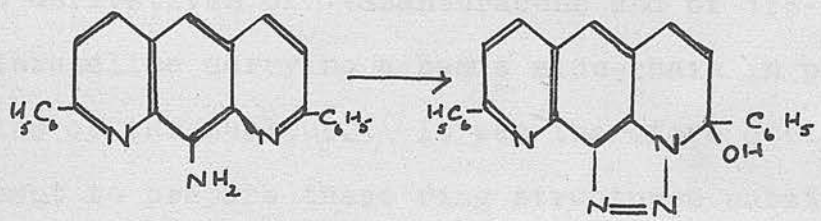
(XXXVI)

He also obtained 2-hydroxy-4:5:8-trimethyl-6:7:2^1:3^1-pyridoquinoline (XXXVII) by a Skraup reaction of 2-hydroxy-4:5:8-trimethyl-6-aminoquinoline (XXXVIII).



(XXXVII) (XXXVIII)

One of the most prolific workers in this field has been Ruggli who, with various colleagues, has synthesised derivatives of 6:7:2^1:3^1- and 6:7:3^1:2^1-pyridoquinoline, or, as they called them, 1:5-and 1:8-anthrazoline, by long series of reactions starting with benzene derivatives and adding on the two pyridine rings. One of these compounds — 9-amino-2:7-diphenyl-1:8-anthrazoline (XXXIX) (Ruggli and Frey, 1939) — is of particular interest with respect to this thesis (see p. 98), as on diazotising with nitrous acid and adding the mixture to alkaline β-naphthol, no coupling takes place, as the diazo compound has already formed a five-membered ring with the peri-ring nitrogen (XL).



(XXXIX) (XL)

During the present research, three general methods have been used in attempts to synthesis derivatives of linear 6:7-benzquinolines:

(1) Skraup reactions on suitable amines.

(2) Condensation of these amines with acetyl acetone and ring-closure of the resulting anils by means of chilled concentrated sulphuric acid (Combes' synthesis).

(3) Condensation of these amines with ethoxy methylene malonate, and ring-closure of the resulting acrylates by various methods.

The work will be discussed under these headings and a fourth subsection will deal with

(4) Attempts to replace the bromine atom of 9-bromo-2:4-dimethyl-1-azanthracene by an amino group or a basic side chain.

Henceforward, linear benzquinolines and pyridoquinolines will be referred to only as 1-azanthracenes and 1:5- and 1:8-anthrazolines.

(1) SKRAUP REACTIONS ON CERTAIN AMINES.

As has been already indicated, it was desired to prepare derivatives of 1-azanthracene and of 1:5- and 1:8-anthrazoline carrying a basis side-chain in position nine of the nucleus. It was therefore decided to attempt to prepare these ring structures substituted in position nine by a bromine atom or an amino group, and then to replace the bromine atom by a dialkylaminoalkylamino side-chain, or to add a dialkylaminoalkyl grouping to the amino group. One of the simplest methods of preparing 9-bromo- and 9-amino-1-azanthracene, and 9-bromo- and 9-amino-1:5-anthrazoline appeared to be to carry out Skraup reactions on 1-bromo- and 1-nitro-/3-naphthylamine and 5-bromo- and 5-nitro-6-aminoquinoline, and then to reduce the two nitro compounds to the corresponding amines. As already described, various workers had found that such experiments yielded not the desired linear compounds, but angular 5:6-benzquinoline or p-phenanthroline. However, in all these Skraup reactions, the traditional method using concentrated sulphuric acid had been employed. As the reaction under these conditions is very drastic, it was decided to repeat these experiments using the modified Skraup reaction as recommended in E.P. 394416, i.e. replacing 96% by

69% sulphuric acid, and using arsenic acid or sodium-m-nitrobenzenesulphonate (Resist Salt) as oxidising agent.

1-nitro-β-naphthylamine was prepared by nitrating N-acetyl-β-naphthylamine as described in Organic Syntheses (1943), and hydrolysing the product with sulphuric acid (Meldola, 1885). The amine was then subjected to a number of Skraup reactions under varying conditions. In the first experiment, a mixture of 1-nitro-β-naphthylamine, 69% sulphuric acid, glycerine and arsenic acid was refluxed for three to four hours until the test for a free amino group was found to be negative. The solution became very black and much tarring took place. The experimental details for the working up of the product are described fully in a later section of this thesis. The only crystalline product isolated from this experiment — pale yellow needles, m.p. 93° — was identified as 5:6-benzquinoline. A Skraup reaction using as low a concentration of sulphuric acid as 69%, thus appeared to eliminate the nitro-group from 1-nitro-β-naphthylamine, and to yield an angular compound. In an attempt to decrease the amount of tarring, this experiment was repeated with ferrous sulphate and boric acid incorporated in the reaction mixture, but again the only product isolated was

5:6-benzquinoline. Finally, it was decided to reduce the strength of the sulphuric acid further to 60% and 50%; in these experiments, no tarring occurred, but no reaction took place, the original 1-bromo-β-naphthylamine being recovered quantitatively. Attempts to prepare 9-nitro-1-azanthracene were thus abandoned, and attention was turned to the preparation of 9-bromo-1-azanthracene.

1-bromo-β-naphthylamine was prepared as described by Lellmann and Schmidt (1887). This compound was then subjected to a Skraup reaction using 69% sulphuric acid, glycerol, arsenic acid and ferrous sulphate. A great deal of tarring occurred, and the only crystalline product isolated was, again, 5:6-benzquinoline. A second experiment was also carried out with 69% sulphuric acid, but using sodium-m-nitro benzene sulphonate, in place of arsenic acid, as oxidising agent. Less tar separated than in the previous experiment, and on working up the reaction mixture, an oil was obtained which failed to crystallise. It was therefore chromatographed using an alumina column as adsorbent. Three products were isolated — the bulk of the material, which passed quickly through the column, proved to be some 5:6-benzquinoline. A very small amount of a pale yellow solid, m.p. 100-124°, was also obtained which gave a

positive Beilstein reaction and a negative diazo test, but the amount was so small (mgs.) that further purification was not possible. Clemo (private communication) has isolated 9-bromo-1-azanthracene from a Skraup reaction on 1-bromo-β-naphthylamine, but in only 1% yield. As the quantity of starting material in the experiments just described was comparatively small, the yellow solid m.p. 100-124°, may have been some bromoazanthracene. The only other product isolated in the last experiment was an oil which failed to crystallise.

Étienne (1946) and Gerhardt and Hamilton (1944) claimed to have prepared 9-chloro-1-azanthracene by Skraup reactions on 1-chloro-β-naphthylamine and its N-acetyl derivative respectively. Accordingly, 1-chloro-β-naphthylamine was prepared as described by Étienne, and then refluxed with a mixture of glycerol, 69% sulphuric acid, arsenic acid and ferrous sulphate until a negative diazo test was obtained. A great deal of tarring took place and a pale yellow crystalline product, m.p. 139-40°, was isolated, but in only 10% yield. Étienne quotes m.p. 140-1°, yield 40%, and Gerhardt, m.p. 138-40°, yield - 34%.

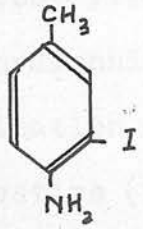
It may therefore be concluded that 9-bromo- and 9-nitro-1-azanthracene cannot be prepared by carrying out Skraup reactions on 1-bromo- and 1-nitro-β-

naphthylamine, and that although 9-chloro-1-azanthracene may be obtained by a similar experiment on 1-chloro-β-naphthylamine, the poor yields obtained during the present work ruled out its use as a practical method from the preparation of 9-chloro-1-azanthracene in quantity.

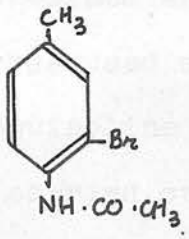
It was suggested by earlier workers that the elimination of the bromine atom or the nitro group in the cases just described took place because of the great tendency towards angular ring-closure under the prevailing experimental conditions. Although this is undoubtedly an important factor, certain observations by Nicolet and others appear to have some bearing on this phenomenon. Thus Nicolet and co-workers (1921 and 1927) found that when certain aromatic compounds having a halogen atom o- or p- to an amino or a hydroxyl group, were boiled with acid, the halogen was replaced by hydrogen, and the solution acquired oxidising properties, as evidenced by the liberation of free halogen, or by the formation of more highly halogenated derivatives. They quote as examples the elimination of what they term "positive" halogen from e.g. 3-iodo-4-aminotoluene (I), 3-bromo-4-acetamidotoluene (II), and 3-iodo-4-hydroxy benzoic acid (III). Other workers have also found evidence of this elimination; thus Schroetier and co-workers (IV),

when reducing 5-bromo-6-hydroxy-7-nitrotetralin (V) with stannous chloride and hydrochloric acid, obtained a mixture of 5-bromo-6-hydroxy-7-aminotetralin (VI) and 6-hydroxy-7-aminotetralin (VII). Sandin and Evans (1939) also observed the bromine of 5-bromo-6-aminotetralin (VIII) to be labile in hot acid solution. During the present research, it was found impossible to obtain 1-iodo-β-naphthylamine (IX) by the acid hydrolysis of 1-iodo-N-acetyl-β-naphthylamine, as the iodine appeared to be liberated in the presence of the acid. Thus under the acid conditions of the Skraup reaction, the bromine atom and the nitro group in the 1-position of β-naphthylamine might be rendered somewhat labile due to their proximity to the amino group, and so their elimination during the process of ring-closure would be facilitated.

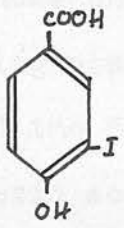
In attempts to prepare derivatives of 1:5- and 1:8-anthrazoline, 5-chloro- and 5-bromo-6-aminoquinoline, and 8-hydroxy-5-methyl-7-aminoquinoline were subjected to Skraup reactions. 5-bromo-6-aminoquinoline was prepared by the following series of reactions. A Skraup reaction was carried out on p-nitraniline (X), 6-nitroquinoline (XI) being obtained in good yield. The latter compound was then reduced to the corresponding 6-aminoquinoline (XII),



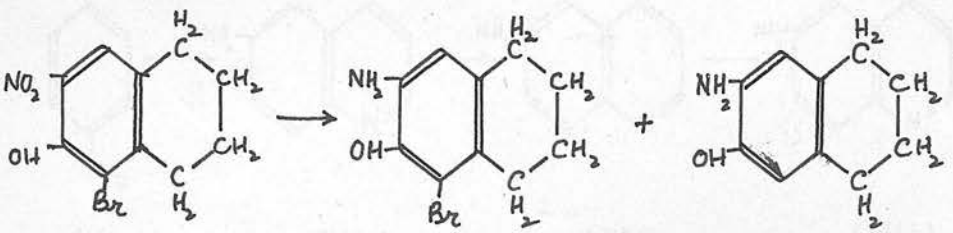
(I)



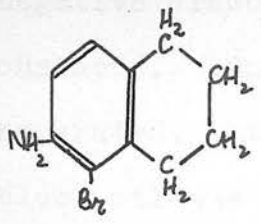
(II)



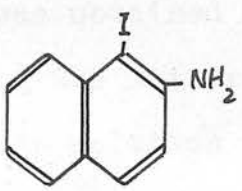
(III)



(V) (VI) (VII)

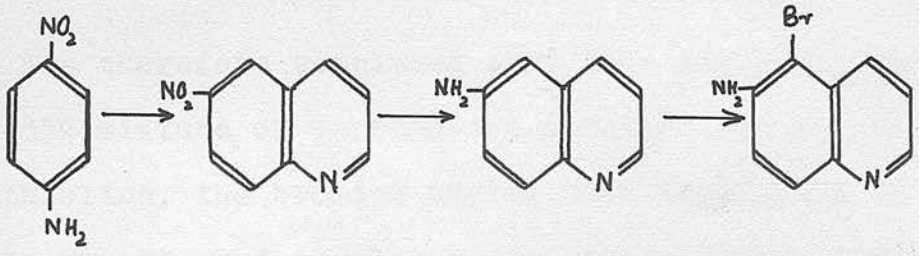


(VIII)



(IX)

the best yield being obtained when stannous chloride and hydrochloric acid was used as reducing agent. Bromination of 6-aminoquinoline to yield the 5-bromo-derivative (XIII) was carried out in acetic acid solution as described in the experimental section of this thesis.



(X) (XI) (XII) (XIII)

In the first Skraup reaction carried out on 5-bromo-6-aminoquinoline using 69% sulphuric acid and arsenic acid, the solution became very black, and a negative diazo test was obtained after refluxing for one hour. On pouring the mixture into water, no tar separated, but when the solution was basified, a black oil was obtained. Two crystalline products were isolated from this oil — white crystals m.p. 175-177°, identified as p-phenanthroline (XIV), and a pale yellow solid which even after several crystallisations from light petroleum melted from 131-133°. This material gave a positive Beilstein reaction and

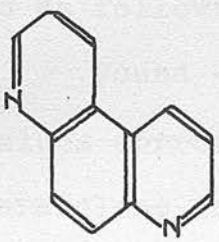
a negative diazo test, and so was thought to be 9-bromo-1:5-anthrazoline (XV). On analysis, however, the following results were obtained -

Found: C - 64.0; H - 4.3; N - 12.3; Br - 21.45.

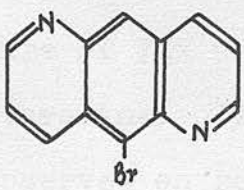
$C_{13}H_7N_2Br$ requires C - 55.6, H - 2.7, N - 10.8, Br. - 30.9.

Calculated for p-phenanthroline, $C_{13}H_8N_2$ — C - 80.0, H - 4.44, N - 15.56.

It was therefore concluded that this material was a 65-35% mixture of 9-bromo-1:5-anthrazoline and p-phenanthroline, the bromine having been eliminated to some extent, and angular ring-closure taking place.



(XIV)



(XV)

In an attempt to effect a more complete separation of the p-phenanthroline and the bromoanthrazoline, the mixture was chromatographed using alumina as adsorbent and benzene as solvent. The colourless

washings which were first collected yielded pure specimens of p-phenanthroline. A yellow band which was adsorbed strongly at the top of the column was eluted with benzene containing a small amount of alcohol, but the yellow solid obtained from these washings, after several crystallisations, yielded a product m.p. 131-3°, identical with the compound described above.

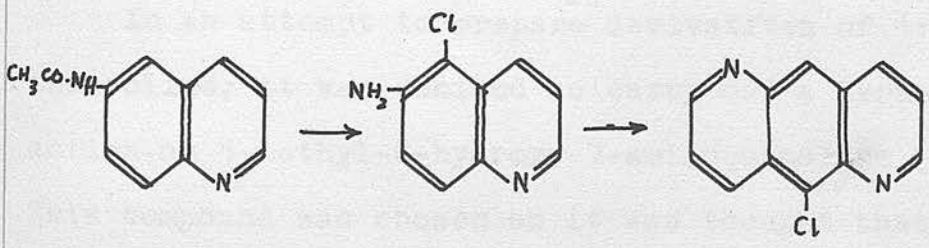
A second Skraup reaction was then carried out on 5-bromo-6-aminoquinoline using sodium-m-nitrobenzene sulphonate as oxidising agent. This time, besides p-phenanthroline, white filamentous needles were obtained which softened at 136° and melted at 140-1°. On cooling the melt and repeating the m.p. determination, a value of 138-9° was obtained. This material analysed as follows -

Found - C - 62.7; H - 3.0.

These values correspond to a mixture of 70% 9-bromo-1:5-anthrazoline and 30% p-phenanthroline. The sharpening of the melting point observed on reheating a melted specimen may have been due to the small amount of p-phenanthroline present subliming, thus leaving pure 9-bromo-1:5-anthrazoline. However, all attempts to remove the p-phenanthroline from the full mixture by sublimation were unsuccessful, extensive decomposition taking place.

As it had been found during experiments in the azanthracene series that the chlorine atom in 1-chloro-β-naphthylamine was less labile than the bromine atom in the corresponding bromo compound, it was decided to attempt to prepare 9-chloro-1:5-anthrazoline (XVI) by a Skraup reaction of 5-chloro-6-aminoquinoline. The only previous record of the preparation of 5-chloro-6-aminoquinoline was that by Kern (1906), who had obtained this compound by heating 5-bromo-6-aminoquinoline with concentrated hydrochloric acid in a sealed tube at 160°. As 5-bromo-6-aminoquinoline had been obtained by the direct bromination of 6-aminoquinoline as described previously, it was decided to attempt the preparation of 5-chloro-6-aminoquinoline in a similar manner. Thus, chlorine was bubbled through an acetic acid solution of 6-aminoquinoline until the desired increase in weight was obtained. The compound isolated in this experiment, m.p. 233°, gave a positive Beilstein reaction but a negative diazo test, and so was not the desired 5-chloro-6-aminoquinoline. 6-amino-quinoline was therefore acetylated, and the resulting 6-acetamidoquinoline dissolved in glacial acetic acid. Various experiments were carried out in which the chlorine was bubbled through the acetic acid solution of the acetyl compound, but it was eventually

found best to collect the desired weight of chlorine in glacial acetic acid, and to add this solution slowly to a well-stirred solution of 6-acetamidoquinoline in the same solvent. The product which was obtained was hydrolysed and recrystallised from water as greyish-white needles m.p. 125-127°, which gave positive tests for halogen and a primary amino group. It was thus concluded to be 5-chloro-6-aminoquinoline. (Kern quotes m.p. 128° for his compound.)



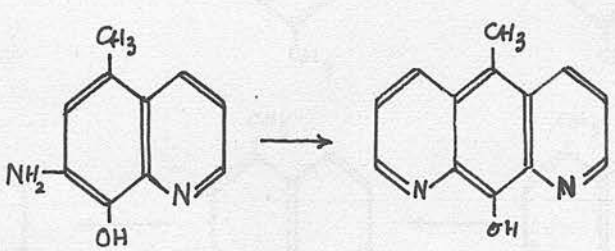
(XVI)

Various Skraup reactions were carried out on this compound. In an experiment using "Resist Salt" as oxidising agent, the only crystalline product isolated was some p-phenanthroline. A red oil was also obtained, which, however, failed to crystallise or to form a crystalline derivative. 5-chloro-6-acetamidoquinoline was then subjected to a Skraup reaction using arsenic acid as oxidising agent, as it was hoped that less

tarring would take place than with the free amine. The mixture still tarred, but no p-phenanthroline was isolated. A very small quantity of yellow needles was obtained pure, which, on analysis, gave values for C and H in accordance with its formulation as 9-chloro-1:5-anthrazoline. The amount obtained, however, did not allow for a N determination, and prevented its use in preparative work.

These experiments in the 1:5-anthrazoline series are thus comparable with those in the 1-azanthracene series, angular cyclization appearing to take place more readily than linear cyclization.

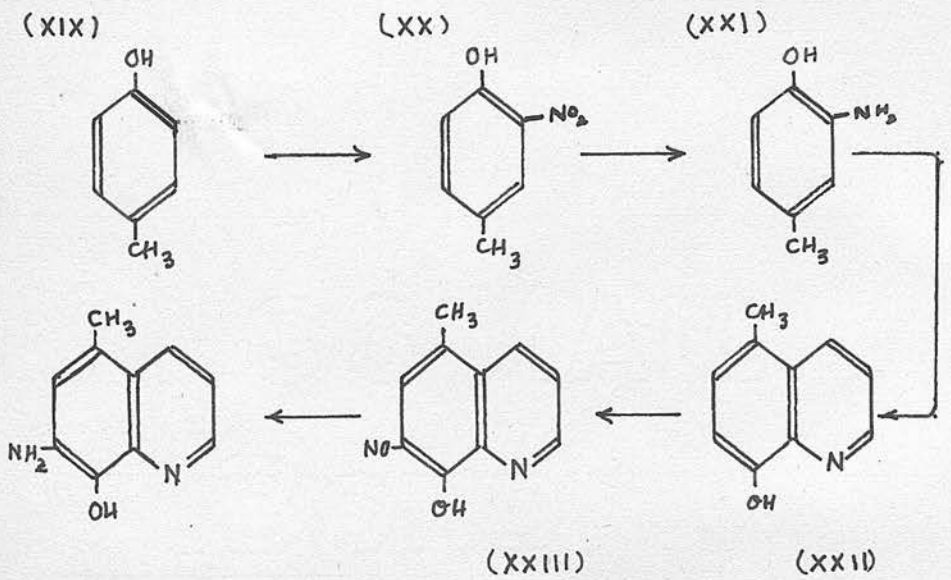
In an attempt to prepare derivatives of 1:8-anthrazoline, it was decided to carry out a Skraup reaction on 5-methyl-8-hydroxy-7-aminoquinoline (XVII). This compound was chosen as it was thought that the 9-hydroxy-10-methyl-1:8-anthrazoline (XVIII) which might result would prove an interesting representative of the "oxine"-like compounds which Albert has shown to have good antibacterial properties.



(XVII) (XVIII)

As these compounds are supposed to act by co-ordination into a chelate five-membered ring of the hydroxyl, the peri-ring nitrogen and a heavy metal which acts as an essential metabolite for the bacterium, 9-hydroxy-10-methyl-1:8-anthrazoline, which offers two possibilities for this type of chelation, should theoretically be an active compound.

5-methyl-8-hydroxy-7-aminoquinoline was prepared by the following series of reactions. p-cresol (XIX) was nitrated to yield o-nitro-p-cresol (XX). This was reduced to the corresponding amine (XXI) by sodium hydrosulphite, and the latter subjected to a Skraup reaction using "Resist Salt" as oxidising agent. The resulting 5-methyl-8-hydroxyquinoline (XXII) was treated with sodium nitrite, when the corresponding 7-nitroso (XXIII) derivative was obtained. This compound was then reduced to 5-methyl-8-hydroxy-7-aminoquinoline by hydrogen sulphide though in poor yield.



A Skraup reaction on the latter compound resulted in a great deal of tarring. A small quantity of yellow solid melting at approximately 240° was isolated, which gave a green colour with ferric chloride, indicative of the presence of a phenolic group, but again the yield was so poor that further purification could not be effected.

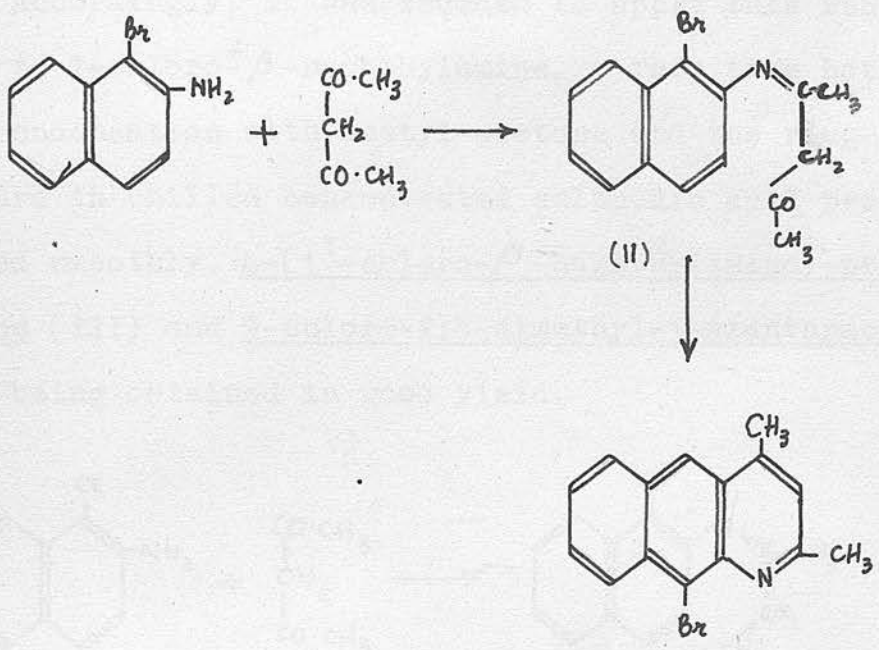
As these linear systems did not appear to be readily formed by Skraup reactions, it was decided to investigate the application of the Combes synthesis which had given such satisfactory results with β - naphthylamine.

(2) THE APPLICATION OF COMBES' SYNTHESIS TO VARIOUS AMINES.

Attention was directed first towards the preparation of 9-bromo-2:4-dimethyl-1-azanthracene (I).

A mixture of 1-bromo-β-naphthylamine, acetyl acetone and anhydrous calcium sulphate was heated on the water-bath as recommended by Johnson and Mathews (1944). A black mass was obtained, from which flesh-coloured needles, m.p. 122-3°, were isolated. This material analysed in accordance with its formulation as 4-(1'-bromo-β-naphthylimino)-pentan-2-one (II). The best yield was obtained on heating the mixture at 50° for one day, or allowing it to stand at room temperature for two days. In both cases a solid mass of large hexagonal crystals was formed, no tarring taking place.

This anil was now added to concentrated sulphuric chilled to 2°, the solution heated to 60° for two minutes, poured on to ice, and basified with 10 N-sodium hydroxide. The resulting 9-bromo-2:4-dimethyl-1-azanthracene was obtained as pale yellow needles, m.p. 169°, in 93% yield.



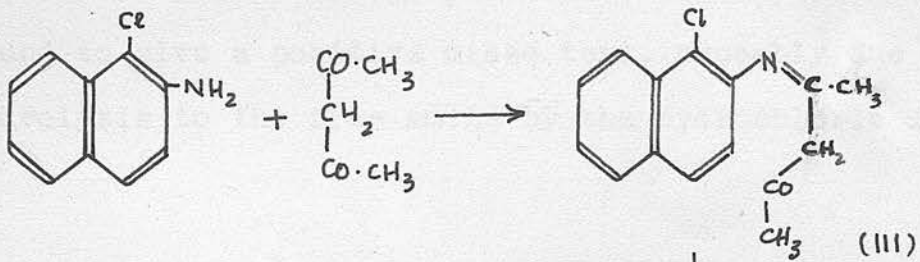
(II)

(I)

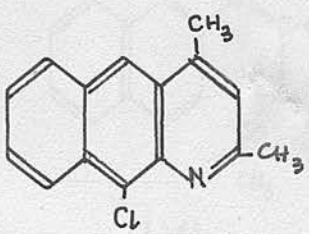
The ease with which this linear benzquinoline is formed and the very good yield obtained is in striking contrast to the results obtained in the Skraup reactions on same amine.

A similar reaction was now carried out with 1-nitro-β-naphthylamine. This time, however, no condensation took place, the nitro-amine being quantitatively recovered. The experiment was repeated using various modifications, e.g. longer periods of heating, higher temperatures, and the introduction of a trace of iodine as catalyst, without success, no condensation being effected. This again is somewhat surprising when compared with the results obtained with 1-bromo-β-naphthylamine.

Accordingly, it was decided to apply this reaction to 1-chloro-β-naphthylamine. This time both the condensation with acetyl-acetone and the ring-closure in chilled concentrated sulphuric acid proceeded smoothly, 4-(1^1-chloro-β-naphthylimino)-pentan-2-one (III) and 9-chloro-2:4-dimethyl-1-azanthracene (IV) being obtained in good yield.



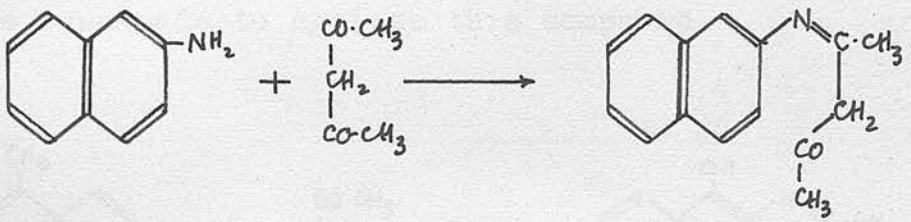
(III)



(IV)

Attempts were now made to synthesise linear anthrazolines using this method. As Johnson and Mathews had reported that unsubstituted β-naphthylamine yielded 1-azanthracene by a Combes' synthesis, it was decided to carry out a similar experiment with 6-aminoquinoline. In the first attempt, the amine — acetyl acetone — calcium sulphate mixture was heated on the water-bath for two hours and then extracted

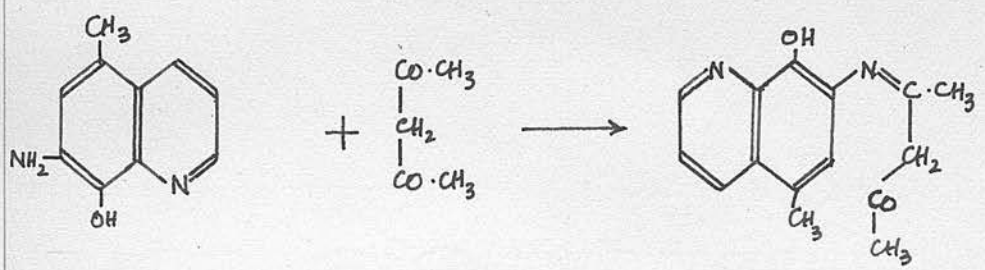
with alcohol. On reducing the volume of the extract, a pale yellow solid m.p. 112-116° was obtained which proved to be the original 6-aminoquinoline, no condensation having been effected. On repeating the experiment, however, using a trace of iodine as catalyst, the condensation proceeded smoothly, and 4-(6¹-quinolylimino-pentan-2-one (V) was obtained as yellow rods, m.p. 105-6° in 76% yield. This compound was found to give a positive diazo test, probably due to hydrolysis to the free amine by the hydrochloric acid.



(V)

Attempts to cyclize this anil by dropping it into chilled concentrated sulphuric acid have proved unsuccessful. Using 96% acid, the only product isolated was some 6-aminoquinoline, hydrolysis having taken place. In a repeat experiment using 100% sulphuric acid, the reaction product was soluble in water, so that it was concluded that sulphonation had taken place.

All attempts to condense 5-bromo- and 5-chloro-6-aminoquinoline with acetyl acetone, even in the presence of iodine, have failed. However, it was found that 5-methyl-8-hydroxy-7-aminoquinoline condensed with ease on heating the amine — calcium sulphate — acetyl acetone mixture on the water-bath for a few minutes, the resulting 4-(5^1-methyl-8^1-hydroxy-7^1-quinolylimino)-pentan-2-one (VI) being obtained as pinkish rods m.p. 184-5° in 75% yield. Unfortunately this material and all the intermediate products were destroyed when a shelf in the laboratory collapsed, and there has not been sufficient time to repeat the rather long preparation, so that, so far, no attempts have been made to cyclize this compound.



(VI)

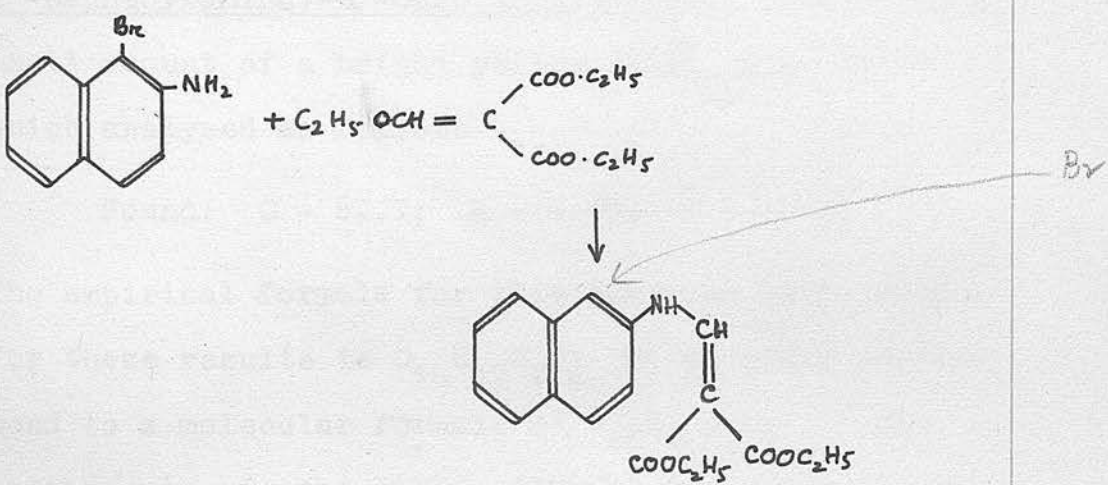
The above results which have been described therefore show that, while the Combes' synthesis does yield linear ring products in certain instances, the inability of some amines to undergo the initial

condensation with acetyl acetone, and the apparent instability of some of the intermediate anils towards sulphuric acid, severely limits its use as a method for the synthesis of linear ring systems generally.

Attention was now turned towards another method for the synthesis of heterocyclic ring systems using ethoxymethylenemalonate.

(3) THE CONDENSATION OF VARIOUS AMINES WITH ETHOXYMETHYLENEMALONATE, AND ATTEMPTS TO RING-CLOSE THE PRODUCTS.

1-bromo-β-naphthylamine was heated with ethoxymethylenemalonate on the water-bath under reduced pressure. The resulting Ethyl-β-(1¹-bromo-2¹-naphthylamino)-α-carbethoxyacrylate (I) was obtained as white rods, m.p. 123-5°, in 97% yield.



(I)

Attempts to cyclize this product, however, have proved disappointing. When the acrylate was dropped into liquid paraffin at 150°, a small amount of oily material, which failed to crystallise, was the only non-tarry material isolated. Using diphenyl as the cyclizing medium, a very dark-brown solid remained on removing the diphenyl by steam distillation.

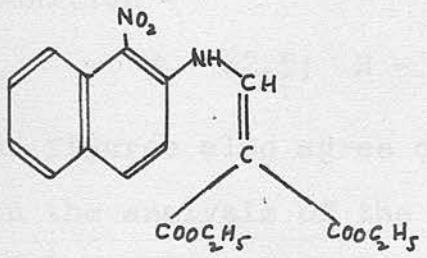
This material was only partially soluble in alcohol and a very small quantity of a light brown gelatinous solid, m.p. 280-5°, was eventually isolated, insufficient for further purification.

On carrying out a similar condensation with ethoxymethylenemalonate using 1-nitro-β-naphthylamine, two products were obtained, orange crystals m.p. 129°, which gave analytical figures agreeing closely with those calculated for ethyl-β-(1¹-nitro-2¹-naphthylamino)-α-carbethoxyacrylate (III), and a small amount of a bright yellow solid, m.p. 231-2°, which analysed as follows -

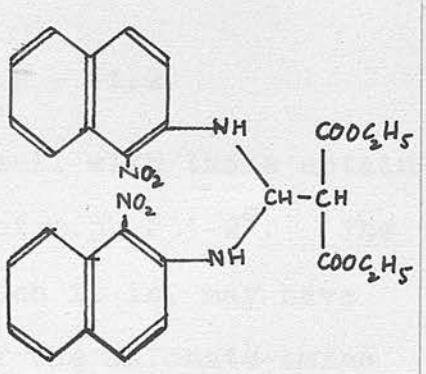
Found: C - 62.2; H - 4.25; N - 10.7.

The empirical formula for this compound calculated for these results is $C_{14}H_{12}N_2O_4$ which would correspond to a molecular formula of $C_{28}H_{24}N_4O_8$. The latter suggests the combination of two molecules of 1-nitro-β-naphthylamine with one of ethoxymethylenemalonate, with the elimination of one molecule of alcohol. This might take place by the addition of the second molecule of 1-nitro-β-naphthylamine to ethyl-β-(1¹-nitro-2¹-naphthylamino)-α-carbethoxyacrylate across the double bond, which would yield a product (III) which would have the following percentage composition -

C - 61.75; H - 4.4; N - 10.3.

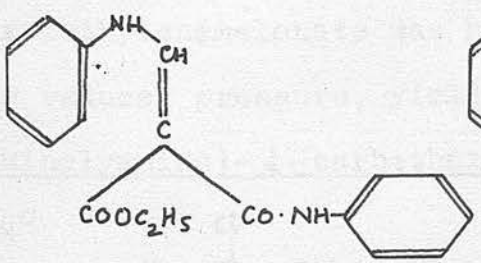


(II)

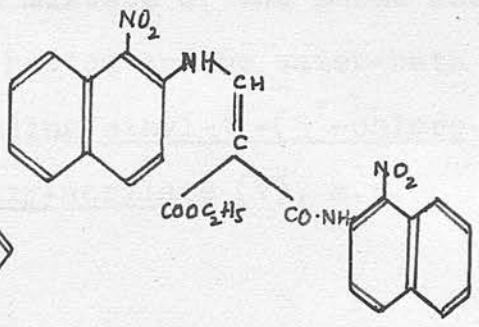


(III)

However, Schofield and Simpson (1946), on condensing aniline and p-anisidine with ethoxymethylene malonate, obtained by-products from the reactions which also gave analytical figures suggesting that two molecules of amine had reacted with one of ethoxymethylene-malonate. Their most likely suggestion for the constitution of this product in the case of aniline was ethyl-α-phenylcarbamyl-β-anilinoacrylate (IV).



(IV)



(IVA)

If the compound isolated in the present experiment

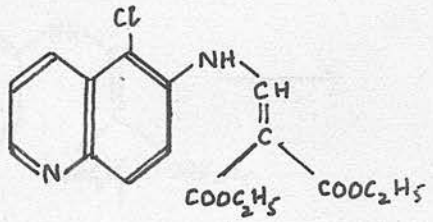
had a similar constitution — ethyl-α-(1^1-nitro-2^1-naphthylcarbamyl)-β-(1^1-nitro-2^1-naphthylamino)-acrylate — it would have the following percentage composition -

C - 62.5; H - 3.8; N - 11.2.

These figures also agree quite well with those obtained in the analysis of the product m.p. 231-2°. The formation of this anilide, if such it is, may have resulted when the temperature of the malonate-amine mixture was raised to 150-170° for a short time. This was done when no solidification had taken place after heating the mixture on the water-bath for two hours, as it was thought that no condensation had been effected.

No attempts have been made, so far, to cyclize ethyl-β-(1^1-nitro-2^1-naphthylamino)-α-carbethoxy-acrylate.

A similar reaction was now carried out with 5-chloro-6-aminoquinoline. A mixture of the amine and ethoxymethylenemalonate was heated on the water-bath under reduced pressure, yielding ethyl-β-(5^1-chloro-6^1-quinolyamino)-α-carbethoxy-acrylate (V), m.p. 153-4°.

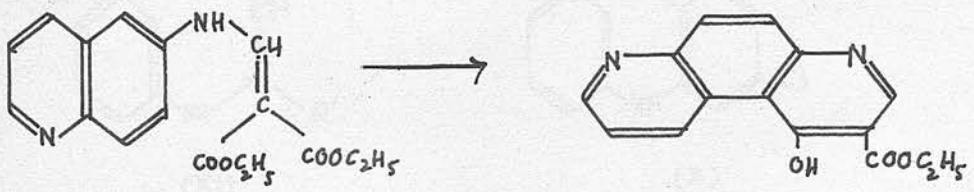


(V)

Attempts to cyclize this compound have proved unsuccessful. Dropping it into boiling diphenyl, and refluxing the mixture for half-an-hour gave a very black solution, and only a very small amount of a greenish yellow solid, m.p. 261-3°, was finally obtained, insufficient for further purification.

Some of the original acrylate was also isolated. When the experiment was repeated, the time of treatment in diphenyl being increased to one hour, the mixture became very black, but a white solid was isolated in considerable quantity which was soluble in water, and was eventually identified as ammonium chloride. This result suggests that very extensive decomposition must have taken place in the mixture. At attempt to cyclize the acrylate by merely heating it in a hard-glass tube was also unsuccessful, the only crystalline product obtained being some of the original acrylate.

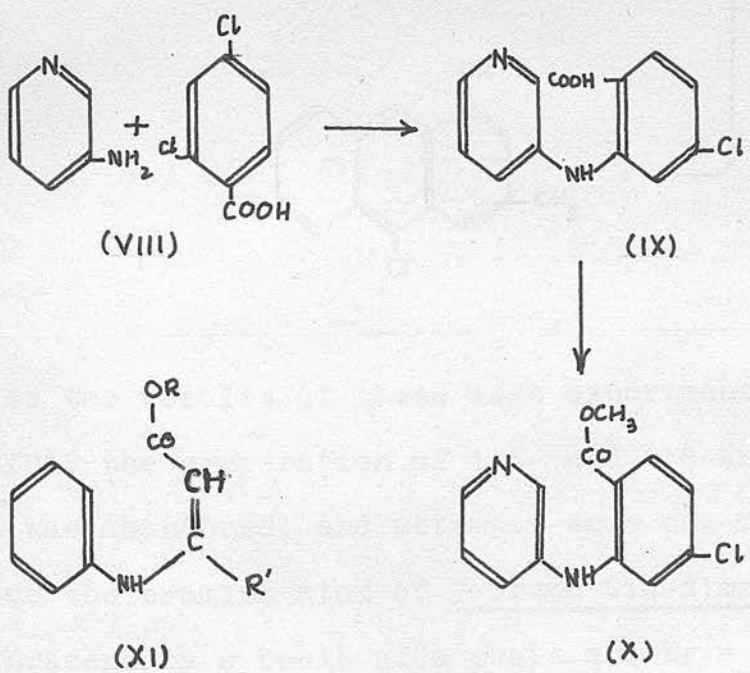
As 6-aminoquinoline condenses with ethoxymethylenemalonate, and the resulting acrylate (VI) cyclizes with ease to give the angular 4-hydroxy-3-carbethoxy-p-phenanthroline (VII) (Douglas and Kermack, 1948),



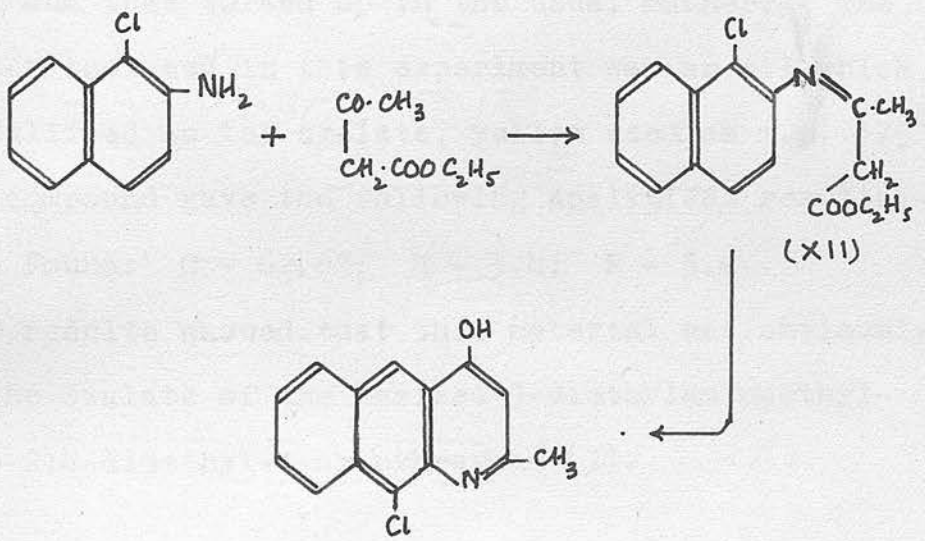
(VI) (VII)

it can only be concluded that when attempts are made to force unnatural linear cyclization by blocking position five of the quinoline nucleus, extensive decomposition takes place.

Results comparable with these just described have been obtained by Price and Roberts (1946), who attempted to prepare 2:3-pyridoquinolines. These workers condensed 3-aminopyridine (VIII) with 2:4-dichlorobenzoic acid, and esterified the intermediate anil (IX) to yield methyl-4-chloro-2-(3^1-pyridylamino)-benzoate (X). Price and Roberts point out that this compound bears a formal resemblance to β-anilino acrylates (XI), but attempts to cyclize it by heating in boiling diphenyl ether were unsuccessful, the original material being recovered.



Inability to cyclize similar acids has also been found by Kermack and Weatherhead (1942). However, it will be recalled that in a somewhat similar case described by Albert et al (1948), the ethyl-β-(1¹-chloro-2¹-naphthylamino)——crotonate (XII) obtained by the condensation of 1-chloro-β-naphthylamine with ethyl acetoacetate was cyclized by dropping into liquid paraffin at 270°, 9-chloro-4-hydroxy-2-methyl-1-azanthracene (XIII) being obtained in 55% yield.



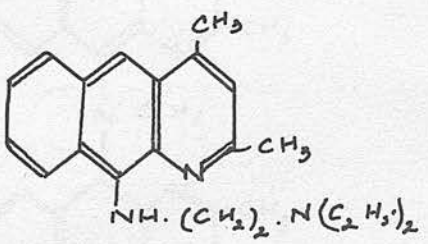
As the results of these last experiments were unfruitful, the preparation of 1:5- and 1:8-anthrazolines was abandoned, and attempts were now made to replace the bromine atom of 9-bromo-2:4-dimethyl-1-azanthracene by a basic side chain and by a simple amino group.

(4) ATTEMPTS TO REPLACE THE BROMINE ATOM OF 9-BROMO-2:4-DIMETHYL-1-AZANTHRACENE BY AN AMINO GROUP OR BY A BASIC SIDE CHAIN.

In the first attempt to replace the bromine atom of 9-bromo-2:4-dimethyl-1-azanthracene by a basic side chain, the traditional method employed in the acridine series of heating a mixture of the amine and the bromo-base, using phenol as solvent, was tried. Accordingly, a mixture of phenol, diethylaminoethylamine and 9-bromo-2:4-dimethyl-1-azanthracene was heated in an oil-bath at 190° for fifteen hours and then worked up in the usual manner. The product isolated in this experiment was an oil which crystallised as the oxalate, yellow needles m.p. 175°. This compound gave the following analytical results:-

Found: C - 62.65; H - 5.4; N - 5.4.

These results showed that this material was obviously not the oxalate of the desired 9-diethylaminoethylamino-2:4-dimethyl-1-azanthracene (I).

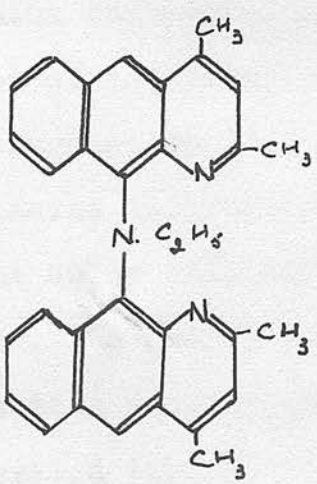


(I)

In a second attempt to effect the condensation, a mixture of 9-bromo-2:4-dimethyl-1-azanthracene, diethylaminoethylamine and alcohol was heated in sealed tube at 180-210° for twenty-four hours, traces of copper bronze and potassium iodide being added as catalysts. Again an oily product was isolated which formed an oxalate - yellow needles, m.p. 181-2°. This compound did not depress the melting point of the compound obtained in the last experiment. The analytical results were also very similar to those obtained for the previous oxalate:-

Found: C - 62.9; H - 5.4; N - 5.75.

Calculation of the empirical formula for these figures gives a value $C_{39}H_{40}N_3O_{12}$, which suggests the presence in the compound of three molecules of oxalic acid and three atoms of nitrogen. One formulation which fits the analysis quite closely is the trioxalate of bis-(2:4-dimethyl-1-azanthracyl)-ethylamine (II).



(II)

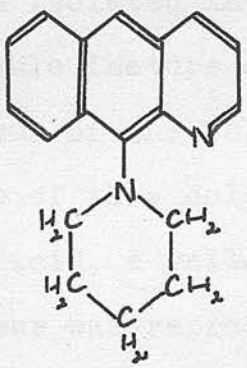
This compound has a molecular formula of $C_{38}H_{35}N_3O_{12}$ and gives calculated values of C - 62.9; H - 4.8; N - 5.8. The hydrogen value here is lower than the analytical values obtained for the oxalate isolated in the experiments described, but if the latter were a tetrahydro derivative of the suggested compound, the calculated values would give quite a close agreement -

Calculated for $C_{38}H_{39}N_3O_{12}$ — C - 62.6, H - 5.35, N - 5.8

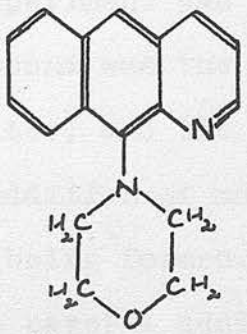
The formation of this compound would entail the combination of two molecules of the azanthracene with one of the amine, the further fission of diethylamine from the side chain, and, if it were the reduced compound, reduction to the tetrahydro derivative.

Evidence was found that decomposition did take place in the sealed tube experiment, a considerable amount of a white, deliquescent, inorganic solid, identified as ammonium carbonate, being formed as a sublimate at the top of the tube. It is intended to try to confirm the suggestion that this oxalate is a bisazanthracylethylamine derivative, by carrying out a similar experiment using ethylamine in place of diethylaminoethylamine. Gerhardt and Hamilton (1944) reported that on heating 9-chloro-1-azanthracene and diethylamine in a sealed tube at 150° for thirty-six

hours using a trace of potassium iodide as catalyst, no reaction took place. In similar experiments using morpholine and piperidine they did obtain 9-(4^1-morpholinyl)- (III) and 9-(1^1-piperidyl)-1-azanthracene (IV), but in only 6% and 8% yields respectively.



(IV)



(III)

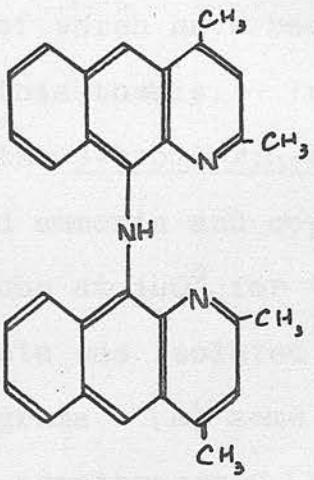
As the direct addition of a basic side chain to the azanthracene nucleus did not appear to be successful, attempts were now made to replace the bromine atom of 9-bromo-2:4-dimethyl-1-azanthracene by an amino group. The first method employed was similar to that used by Haworth and Sykes (1944), a mixture of the azanthracene, phenol and concentrated ammonia, with a trace of copper sulphate as catalyst, being heated in a sealed tube at 300° for three days. A great

deal of tarring occurred, and a small amount of a dark-red hydrochloride m.p. 285° was the only crystalline product isolated. A second experiment was therefore carried out, a mixture of the azanthracene, concentrated ammonia and copper bronze being heated in a sealed tube at 200-230° for twelve hours. Less tarring occurred, and some of the same dark-red hydrochloride isolated in the last experiment was obtained. One notable feature of this compound was the blood-red colour of the solution in water, and the disappearance of this colour on the addition of more hydrochloric acid, a yellow solution being formed. The red colour was reproduced on the careful addition of ammonia, so it appeared that the colour change from red to yellow was due to the formation of a higher hydrochloride.

On making an aqueous solution of this hydrochloride alkaline with ammonia, an orange solid was obtained, m.p. 125-126°, which analysed as follows:-

Found: C - 83.9; H - 5.9; N - 9.7.

This was obviously not 9-amino-2:4-dimethyl-1-azanthracene (V) which requires C - 81.1, H - 6.3, N - 12.6. The analytical figures, however, agree quite closely with those calculated for <u>bis-(2:4-dimethyl--1-azanthracyl) amine</u> (VI) which requires C - 84.3, H - 5.85, N - 9.8.



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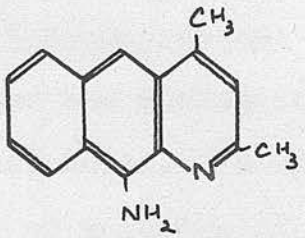


(V)

The formation of this compound, which entails the combination of two molecules of the azanthracene with one of ammonia, is comparable to the results obtained in the attempts to replace the bromine atom of 9-bromo-2:4-dimethyl-1-azanthracene by diethylaminoethylamine, (see p. 94) when a compound was obtained which analysed in accordance with its formulation as bis-(2:4-dimethyl-1-azanthracyl)-ethylamine (II).

When the red hydrochloride of the compound obtained in the present experiment was treated with sodium nitrite, the red colour disappeared, but no coupling took place in alkaline β-naphthol. This is in agreement with its formulation as bis-(2:4-dimethyl-1-azanthracyl) amine, the disappearance of the red colour corresponding to the formation of a nitroso derivative.

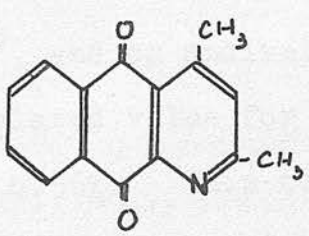
Two other experiments were carried out, full

details of which have been given in the experimental part of this thesis. In the first of these, a mixture of the 9-bromo-2:4-dimethyl-1-azanthracene, concentrated ammonia and copper bronze was heated in a sealed tube at 140° for twenty-four hours. A variety of products was isolated by means of a series of chromatograms - (a) some unchanged 9-bromo-2:4-dimethyl-1-azanthracene, (b) some of the product m.p. 125-126° which has been identified as bis-(2:4-dimethyl-1-azanthracyl) amine (VII), (c) a small amount of a quinone, probably 2:4-dimethyl-1-azanthraquinone (VIII), (d) some 2:4-dimethyl-1-azanthracene.

The minute yield of the material, which was thought to be 2:4-dimethyl-1-azanthraquinone, prevented complete purification being effected, and the final melting point recorded was less than that of the pure compound; however, a purple vat was obtained with sodium hydrosulphite, indicating the presence of a quinone structure, and the compound was found to contain no halogen, so it was thought that it was most likely 2:4-dimethyl-1-azanthraquinone. The formation of 2:4-dimethyl-1-azanthracene resulted by a simple replacement of the bromine atom by hydrogen. This reduction of part of the bromo-azanthracene may be associated with the oxidation of another part of the corresponding quinone (VIII).

Finally, an attempt was made to replace the bromine atom by an amino group by a method similar to that used by Albert in preparing 4-amino-1-azanthracene derivatives (see p.54). Ammonia was slowly passed into a solution of 9-bromo-2:4-dimethyl-1-azanthracene in phenol, a trace of copper bronze being added as catalyst. Most of the original base was recovered, however, the only other product being a small quantity of oil which yielded no crystalline derivative.

During the course of the work just described, it was thought that an iodine atom in the nine position of the azanthracene nucleus might be more easily replaced by a basic side chain than would a bromine atom in the same position. It was therefore decided to try to prepare 9-iodo-2:4-dimethyl-1-azanthracene by a Combes' synthesis on 1-iodo-β-naphthylamine. However, all attempts to prepare 1-iodo-β-naphthylamine, which will now be described, were unsuccessful.



(VIII)

(5) ATTEMPTS TO PREPARE 1-IODO-β-NAPHTHYLAMINE.

Willstaedt and Schreiber (1934) claimed to have prepared 1-iodo-β-naphthylamine, by iodinating N-acetyl-β-naphthylamine with iodine monochloride, and hydrolysing the resulting 1-iodo-N-acetyl-β-naphthylamine, by boiling with concentrated hydrochloric acid for three hours. They report that the amine crystallised from water as shining, silvery leaflets, m.p. 108°, which, on analysis, gave a nitrogen content of 5.21%, the calculated value being 5.29%. An experiment was therefore carried out, using the conditions recommended by these workers. A solution of iodine monochloride in glacial acetic acid was added slowly and with stirring to a solution of N-acetyl-β-naphthylamine in the same solvent. The mixture was allowed to stand for one hour, and then poured into water. A brownish solid separated which was filtered, washed and recrystallised from alcohol, yielding white needles m.p. 164°. The product obtained by Willstaedt and Schreiber at this point darkened at 160°, melted at 167°, and on analysis, gave a N value of 4.56%; the calculated value for 1-iodo-N-acetyl-β-naphthylamine is 4.56%. This compound was now dissolved in alcohol, concentrated hydrochloric acid slowly stirred in, and the mixture refluxed for three hours. Violet vapours filled the flask and escaped

through the condenser. The vapours were identified as free iodine, as on testing with starch solution, a deep blue colour was produced. The mixture was allowed to stand over night, and in the morning the flask was found to be filled with a black crystalline mass. This was filtered off and extracted with boiling ammonium hydroxide. A thick black oil formed which was insoluble in the ammonia, and which was separated from the ammoniacal liquors by decantation. The latter, on cooling, deposited shining, white plates, m.p. 108°, which after crystallisation from alcohol melted at 110-112°. This material gave a positive diazo test, but a negative Beilstein reaction, and did not depress the melting point of an authentic specimen of β-naphthylamine. It thus appeared that on acid hydrolysis of the acetyl compound that the iodine was being removed and that β-naphthylamine was being formed. The black oil gave a very black solution in alcohol, smelling strongly of iodine.

This elimination of iodine is not surprising in the light of Nicolet's work, discussed earlier in this thesis (see p. 69), on the lability, under acid conditions, of halogen atoms situated o- or p- to an amino group. The description of the compound, obtained by Willstaedt and Schreiber, which they claim to be 1-iodo-β-naphthylamine, is very similar to the

appearance of β-naphthylamine when crystallised from water, and the melting points are very close. However, β-naphthylamine contains 9.7% nitrogen as against the 5.21% quoted by Willstaedt and Schreiber, so that these results cannot be reconciled. It is to be noted that these workers do not seem to have carried out an iodine determination on their compound, nor do they refer to any qualitative test which they did for iodine.

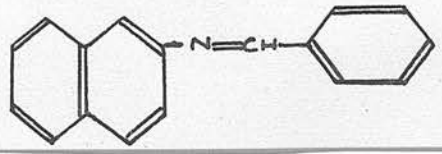
The stability of iodine in 1-iodo-N-acetyl-β-naphthylamine towards acid was further tested by preparing a 5% solution of the pure acetyl compound, and to one part of this solution, adding nine parts of N/10, N, and 2 N. hydrochloric acid respectively. A trace of starch solution was added to two sets of these solutions, then one set was kept at room temperature, and one placed in an incubator at 37°. The incubated tubes containing the N and 2 N acid produced a blue colour over night, as did the tube containing the N/10 acid six hours later. After three days, the tube containing N and 2 N acid, which were kept at room temperature, turned blue, and at the end of a week, the N/10 tube also showed a blue colouration. These experiments indicate that the iodine in 1-iodo-N-acetyl-β-naphthylamine is unstable to acid, even in the cold, so that it is difficult to understand

how Willstaedt and Schreiber obtained 1-iodo-β-naphthylamine under the experimental conditions they employed.

Attempts were now made to obtain 1-iodo-β-naphthylamine by hydrolysing the acetyl compound with alcoholic potassium hydroxide. The main product of this reaction was a white solid, m.p. 128-30°, which was identified as N-acetyl-β-naphthylamine. An oil was also obtained which gave a positive diazo test and a positive Beilstein reaction, but all attempts to crystallise it failed. It would seem from this that treatment with alkali also removes the iodine, to some extent at least.

It was therefore decided to attempt to prepare 1-iodo-β-naphthylamine by the direct iodination of β-naphthylamine, when the necessity for hydrolysis would be avoided. Using iodine as the iodinating agent, no reaction took place, β-naphthylamine being recovered unchanged. When iodine monochloride was used, only some of the original β-naphthylamine was recovered, a black oil also being formed which yielded no crystalline product.

A different line of approach was then tried. Benzal-β-naphthylamine (IX) was prepared by treating β-naphthylamine with benzaldehyde in alcohol solution at 70°. This compound was then dissolved



(IX)

in chloroform, and a solution of iodine monochloride in chloroform added. A yellow solid was precipitated, which, on treatment with sodium hydroxide, yielded a brown oil. A portion of this oil was benzoylated, yielding a compound, m.p. 153°, which gave a positive Beilstein reaction. Analysis, however, showed that it contained less than 1% of iodine. A portion of the oil was also treated with acetic anhydride in the cold, a small quantity of white crystals being obtained, m.p. 164°, identical with 1-iodo-N-acetyl-β-naphthylamine. It thus appears that this oily product does contain at least some 1-iodo-β-naphthylamine, which itself may possibly be oily in character.

Further attempts to crystallise the oil resulted only in the recovery of some of the original Benzal-β-naphthylamine, no further crystalline products being obtained.

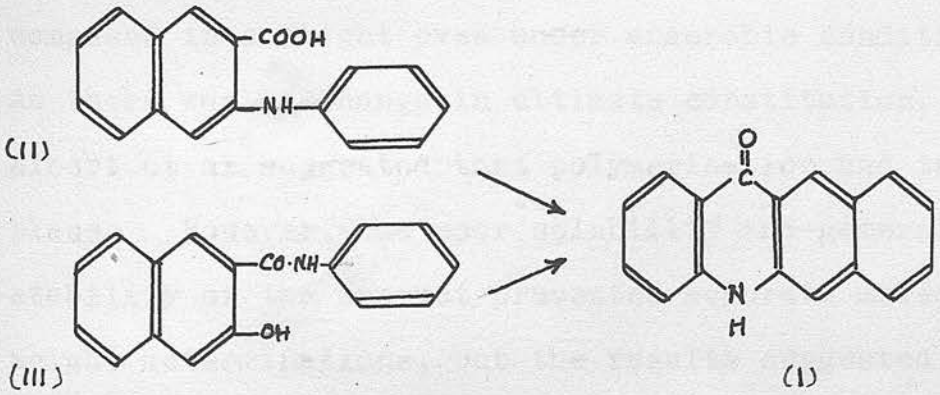
Finally, it was decided to prepare phthalimido-β-naphthylamine, and to attempt to iodinate it by treatment with iodine monochloride. The phthalimido group would then be removed by the hydrazine hydrate method, drastic acid conditions being avoided. It was found best to prepare phthalimido-β-naphthylamine by heating phthalic anhydride and β-naphthylamine in nitrobenzene solution. Without the solvent,

the phthalic anhydride tended to sublime. All attempts to iodinate this compound, however, by treatment with iodine monochloride failed, no reaction taking place and the original compound being recovered.

The preparation of 1-iodo-β-naphthylamine had thus to be abandoned.

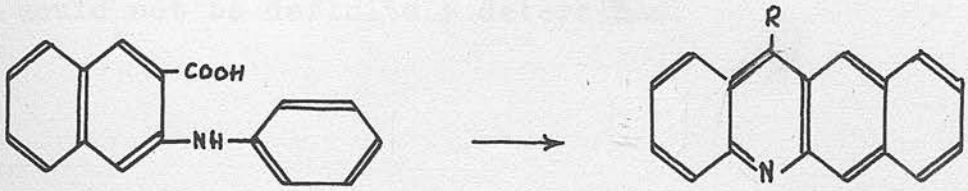
(B) THE SYNTHESIS OF DERIVATIVES OF 2:3-BENZACRIDINE.

The earliest record of work on derivatives of 2:3-benzacridine is that by Schöpff (1892 and 1893), who prepared 2:3-benzacridone (I) by heating 3-anilino-2-naphthoic acid (II) or its anilide at 180° with concentrated hydrochloric acid, and by fusing 3-hydroxy-2-naphthanilide (III) with zinc chloride.



Albert, Brown and Duewell (1948) repeated this work but found that the yields were very poor. The object of the latter research was to obtain 5-amino-2:3-benzacridine (IV), which was eventually prepared in the following way:- 3-anilino-2-naphthoic acid was cyclized by treatment with phosphorous oxychloride. The 5-chloro-2:3-benzacridine (V) which was obtained was heated with ammonium carbonate in phenol at 120°, when the chlorine atom was replaced by an amino group.

(V) R = Cl
(IV) R = NH_2

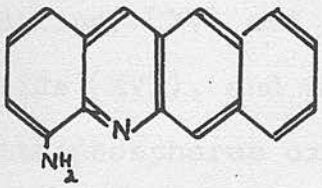


(V) & (IV)

5-amino-2:3-benzacridine was found to be rapidly decomposed in sunlight even under anaerobic conditions. As there was no change in ultimate constitution, Albert et al suggested that polymerisation had taken place. However, the poor solubility and general instability of the product prevented accurate molecular weight determinations, but the results suggested that the compound was a dimer of 5-amino-2:3-benzacridine. During the present work, it was found that the chlorobenzacridines prepared were light-sensitive, and on being exposed to sunlight underwent colour changes, but so far, this phenomenon has not been examined in detail.

Bachmann and Cowen (1948) attempted to prepare 1-amino- (VI) and 9-amino-2:3-benzacridine (VII) but in the 1-amino series, the yields of the intermediate compounds were so poor that the final stages were not carried out, and although a compound presumed to be

9-amino-2:3-benzacridine was obtained, the amount was insufficient for analysis and so its constitution could not be definitely determined.



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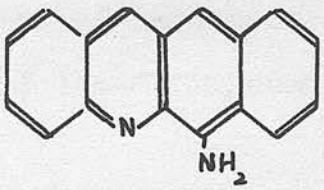
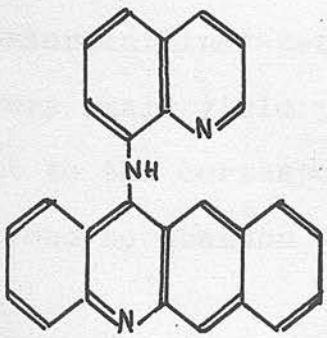


(VI)

However, they did prepare 5-(6^1-methoxy-8^1-quinolylamino)- (VIII) and 7-methoxy-5-(diethylaminopropylamino)-2:3-benzacridine (IX) which were found to have no antimalarial activity. The intermediate 5-chloro and 7-methoxy-5-chloro-2:3-benzacridines were prepared by cyclizing 3-anilino-2-naphthoic acid and 3-(p-anisidino)-2-naphthoic acid respectively with phosphorus oxychloride, the latter being obtained by an Ullmann condensation using 3-bromo-2-naphthoic acid and p-anisidine. The chlorine atoms in the five positions were then replaced by the respective side chains.



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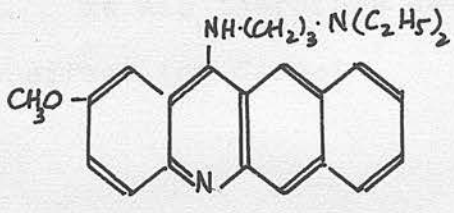
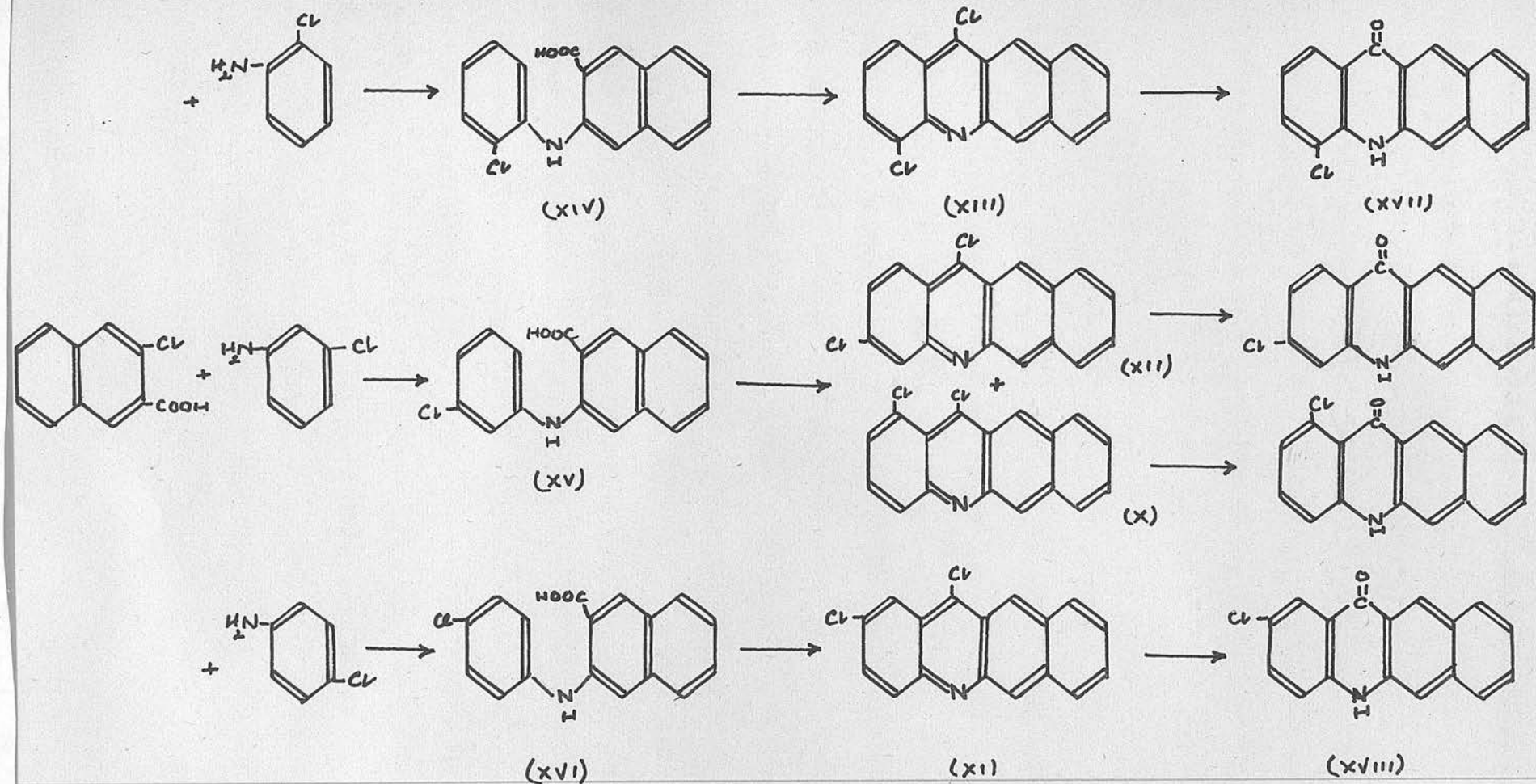


(IX)

As has already been mentioned, part of the work of this research was the preparation of 5:6- (X), 5:7- (XI), 5:8- (XII) and 5:9- (XIII) dichloro-2:3-benzacridines. The general scheme followed was the formation of 2-(o-chloroanilino)-(XIV), 2-(m-chloroanilino)-(XV) and 2-(p-chloroanilino)-3-naphthoic acids (XVI), and the cyclization of these compounds with phosphorus oxychloride.

In the first attempt to prepare 3-(m-chloroanilino)-2-naphthoic acid, a mixture of 2-hydroxy-3-naphthoic acid and m-chloroaniline was heated under reflux for five hours. A similar experiment with aniline had been carried out by Bachmann and Cowen (1948) and Albert, Brown and Duewell (1948), the former workers obtaining 3-anilino-2-naphthanilide in 45% yield, while Albert et al could only obtain a yield of 10% of theory. In the present experiment, the heated mixture became very black, tarred, and on cooling, set to a solid black mass. On working up this material in a manner similar to that used by Bachmann, a very small amount of a greenish-yellow solid was obtained, which may have been some 3-(m-chloroanilino)-2-naphth-m-chloroanilide, but the very small yield precluded any attempt to hydrolyse it to the corresponding acid. It was therefore decided to abandon attempts to effect the direct


Cl
H_2N
HOOC
N
H
(XIV)
(XIII)
(XVII)
COOH
(XV)
(XII)
(X)
(XVI)
(XI)
(XVIII)

condensation of 3-hydroxy-2-naphthoic acid with m-chloroaniline, and to prepare the desired anilino-acid by an Ullmann condensation using 3-chloro-2-naphthoic acid and m-chloroaniline (Ullmann, 1907).

Two nethods of preparing 3-chloro-2-naphthoic acid are recorded in the literature, one by Hosaeus (1893), and the other by Strohbach (1901). Hosaeus mixed one part of 3-hydroxy-2-naphthoic acid with ten parts of phosphorus pentachloride and distilled the mixture, until, as he says, it was completely decomposed. The temperature of the reaction mixture was not recorded. He observed that phosphorus oxychloride began first to distil, followed by phosphorus pentachloride, a pale yellow oil and then a dark-coloured product. The distillation was stopped when the latter material began to distil, and the distillate was treated with water. The heat produced by the decomposition of the phosphorus pentachloride and oxychloride effected the hydrolysis of the 3-chloro-2-naphthoyl chloride, a yellow crystalline mass of 3-chloro-2-naphthoic acid being obtained. The residue in the flask also yielded the same material m.p. 216°. However, no yield was quoted for this experiment.

Strohbach heated a mixture of 3-hydroxy-2-naphthoic acid (1 mole) with phosphorus pentachloride

(3 moles) in an oil bath at 200-210°, the phosphorus oxychloride formed during the reaction being allowed to distil over. When no more oxychloride was produced, the residue was subjected to a vacuum distillation under a pressure of 160 m.m. at 220-260°, and various fractions collected. A thick, refractive oil with a spicy smell distilled at 248° which, on solidifying, was found to melt at 56.5°. The yield quoted for this experiment was 49.3% of theory. On heating with water, the acid-chloride was hydrolysed yielding 3-chloro-2-naphthoic acid m.p. 216°.

In the first attempt to prepare 3-chloro-2-naphthoic acid, a mixture of the hydroxy acid and phosphorus pentachloride was heated in an oil-bath at 200°. Phosphorus oxychloride and pentachloride distilled over, but no pale yellow oil, as described by Hosaeus, was observed. The mixture became very black and if heated for a long time, or if the temperature rose above 220°, formed a black crusty solid. When all the phosphorus oxychloride had distilled over (2-3 hrs.), the black oily residue was poured into water. On warming the mixture slightly on the water-bath, the oil solidified to a dark-brown solid which proved very difficult to purify. It was finally found best to extract this material with cold ether, 3-chloro-2-naphtoic acid being obtained almost

pure on removing the solvent, but in only 25% yield. On decomposing the oxychloride-pentachloride distillate, only a very small amount (mg.) of the acid was obtained.

An experiment was now carried out along the lines suggested by Strohbach. The oily residue after all the phosphorus oxychloride had distilled over, was distilled under 20 m.m. pressure. A great deal of charring took place, and only a small amount of a colourless oil distilled at 235-40°. This oil solidified in the condenser to a white solid, which, on warming with water, gave a very pure specimen of 3-chloro-2-naphthoic acid m.p. 216°. This method, however, because of the extensive charring, was of no practical value for the preparation of the acid in quantity.

It was thus decided to modify the method used by Hosaeus, so as to avoid, as far as possible, the formation of tarry by-products and to improve the yield of 3-chloro-2-naphtoic acid. A similar experiment was therefore carried out using phosphorus oxychloride as solvent. The mixture of 3-hydroxy-2-naphthoic acid, phosphorus pentachloride and phosphorus oxychloride was refluxed for six hours in an oil-bath at 130°, and the phosphorus oxychloride then distilled off. The dark-brown oil which remained was poured

into water. On warming the mixture, the oil dissolved almost completely, only a small amount of a pale yellow solid, which proved to be 3-chloro-2-naphthoic acid, being insoluble. This was filtered off and the filtrate heated on the water-bath in evaporating basins. The pale yellow crystalline mass which deposited in quantity was found to be unchanged 3-hydroxy-2-naphthoic acid, chlorination having been effected only to a very small extent. It was thus decided to raise the temperature of the reaction mixture. On carrying out an experiment at 170°, a better yield (60%) of the chloro acid was obtained, but again the product was difficult to purify due to the formation of tarry by-products. However, when a trace of cetyltrimethylammonium bromide (cetablon) was included in the reaction mixture, 3-chloro-2-naphthoic acid was obtained in 73% yield. The use of the 'cetablon' was suggested by a patent of the American Cyanamide Company, which stated that in the formation of anilides from 3-hydroxy-2-naphthoic acid and aromatic amines using phosphorus trichloride as condensing agent, the extent of the formation of tarry by-products was reduced, and the quality of the product improved by the addition of a small amount of a surface active agent such as sodium dioctyl succinate. As the only compound of this

type available in the laboratory was cetyl trimethyl ammonium bromide, a little of this was added to the hydroxy-acid, phosphorus pentachloride, phosphorus oxychloride mixture with successful results. In addition to the improved yield of the chloro acid, the main effect was the elimination of tarring, so that the acid was obtained almost pure immediately after treating the reaction mixture with water.

3-chloro-2-naphthoic acid was now condensed in turn with o-, m- and p-chloroanilines, by refluxing a mixture of the acid, the respective amine, anhydrous potassium carbonate, amyl alcohol, and copper-bronze, which acted as a catalyst, in an oil-bath at 160° for six hours. In preliminary experiments it was found that the mixtures became quite dark, and on cooling, a greenish-yellow solid separated in all three cases. This was filtered, washed with acetone and extracted thoroughly with hot dilute potassium carbonate solution. On acidifying the extract with acetic acid, a pale yellow solid separated, which, after purification, melted at approximately 220°, gave a negative Beilstein reaction, a deep blue colour with a 1% solution of ferric chloride and was finally identified as 3-hydroxy-2-naphthoic acid, a mixed melting point with an authentic specimen of this material being unchanged. It was therefore

concluded that some of the 3-chloro-2-naphthoic acid had been hydrolysed to the corresponding hydroxy acid.

The amyl alcohol filtrates and the acetone washings from the three condensations were now steam distilled. The distillate in all three cases was found to give a positive diazo test, and in the experiment using p-chloroaniline, a white solid, identified as some of the original amine, solidified in the condenser. The black oils which remained in the flasks after the distillation had finished were thoroughly extracted with hot potassium carbonate solution and filtered. On acidifying the hot filtrates with acetic acid, a bright, canary yellow solid separated in each case, but in small quantity. The filtrates from these solids, on acidifying with concentrated hydrochloric acid, gave copious pale yellow precipitates, which were found to contain halogen and, after purification, melted at 216°. This material was identified as some unchanged 3-chloro-2-naphthoic acid.

The canary yellow solids obtained in the three experiments were purified by re-extraction with hot potassium carbonate solution, acidification with acetic acid and crystallisation from benzene and alcohol. On analysis they gave results in accordance with their formulation as 3-(o-chloroanilino)-

2-naphthoic acid (XIV), m.p. 228-30°, 3-(m-chloroanilino)-2-naphthoic acid (XV), m.p. 227-9°, and 3-(p-chloroanilino)-2-naphthoic acid (XVI), m.p. 244-246°. It was found difficult to obtain sharp melting points, the compounds always melting over a range of 2°. The yield of these acids, in every case, was exceptionally poor, 5 g. of 3-chloro-2-naphthoic acid yielding, on an average, ½ g. of condensation product. The experiments were therefore repeated, a trace of potassium iodide being added as catalyst. The yields of the anilino acids were found to be greatly improved. As before, some 3-hydroxy-2-naphthoic acid was formed, and some of the original chloro acid and the amine were recovered unchanged, but the bulk of the material was converted to the anilino acids, the yields in the three cases being 3-(o-chloroanilino)-2-naphthoic acid - 60%, 3-(m-chloroanilino)-2-naphthoic acid - 72%, and 3-(p-chloroanilino)-2-naphthoic acid - 60%.

These intermediate acids were now cyclized by heating with phosphorous oxychloride for two hours in an oil bath at 150°. Most of the excess phosphorous oxychloride was distilled off and the dark-purple residue poured into a mixture of ice, chloroform and concentrated NH_3. In the experiment with 3-(o-chloroanilino)-2-naphthoic acid, the chloroform layer

became a pinkish-orange colour, and a green fluorescence was observed. The chloroform layer was separated, washed with water, and dried over anhydrous sodium sulphate. On distilling off the chloroform a deep orange-red solid remained which, after several crystallisations from benzene and light petroleum (60-80°), melted at 203°. Analytical figures agreed with its formulation as 5:9-dichloro-2:3-benzacridine (XIII). When this compound was heated on the water bath with 2 N-hydrochloric acid, the red colour disappeared after approximately five minutes, and an orange solid was formed. Heating was continued for half-an-hour, and the solid was then filtered off, washed and crystallised from alcohol as yellow needles, m.p. approximately 270°. This compound was found to be moderately soluble in ether and benzene, giving yellow solutions with a green fluorescence, and was finally crystallised for benzene as needles, m.p. 271-2°. Analytical figures were obtained agreeing with its formulation as 9-chloro-2:3-benzacridone (XVII). The comparatively low melting point of this product, and its solubility in ether and benzene is rather surprising as many acridones having melting points over 360°, are only very sparingly soluble in these solvents.

The dark purple residue from the cyclization of

3-(p-chloroanilino)-2-naphthoic acid (XVI), on pouring into the ice, chloroform, ammonia mixture, coloured the chloroform orange-brown and a green fluorescence was observed. The chloroform layer was separated, washed, dried, and the solvent distilled off. An orange solid remained which crystallised from benzene as reddish-orange crystals m.p. 227-9°. After drying in vacuo over phosphorus pentoxide for six hours, however, the melting point was raised to 239-240°. The analytical figures for this compound agreed with those calculated for 5:7-dichloro-2:3-benzacridine (XI). When heated on the water-bath with dilute sulphuric acid or dilute hydrochloric acid, this compound was converted to 7-chloro-2:3-benzacridone (XVIII), m.p. $>360^{\circ}$.

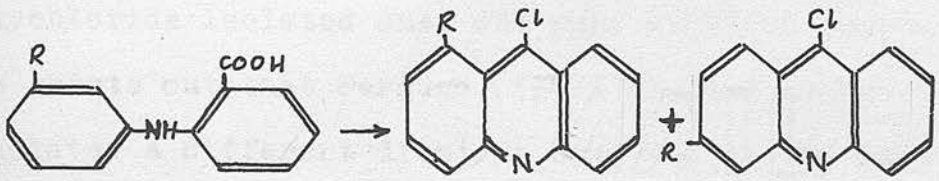
3-(m-chloroanilino)-2-naphthoic acid (XV) when treated with phosphorus oxychloride may cyclize in two positions to give 5:6- (X) and 5:8-dichloro-2:3-benzacridine (XII). It was therefore expected that a mixture of these isomers would be obtained in the cyclization of this acid, and this was indeed found to be the case. On working up the dark-purple residue in a manner similar to that described for the o- and p-isomers, an orange colour was produced in the chloroform, and a greenish fluorescence was observed. This layer was separated, washed, dried,

and, after removing the solvent, the residual reddish-orange solid was fractionally crystallised from dry benzene. Four fractions were collected; the first fraction consisted of light orange needles melting at approximately 210-20°. Further crystallisation from light petroleum raised the melting point to 231-2°, decomposition taking place on melting. The analytical figures for this compound agreed with those calculated for a dichloro-benzacridine. The second fraction consisted of reddish-orange needles melting approximately from 180-200°, and the third, a deep reddish-orange solid melting from 150-165°. The fourth fraction was merely a dark-brown, amorphous mass which was extremely soluble in benzene and appeared to be tarry in nature. It was found that the second and third fractions could not easily be purified by crystallisation, so it was decided to chromatograph the mixed fractions.

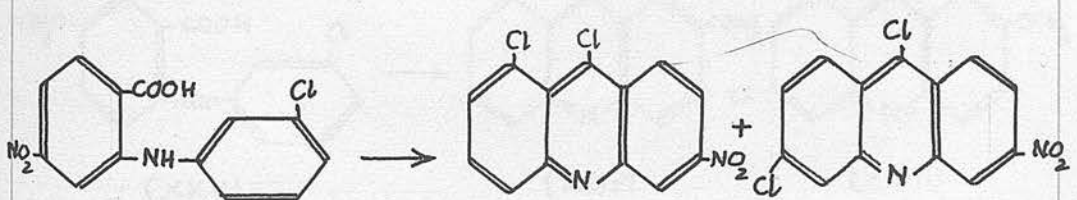
The mixture was dissolved in benzene and passed into an alumina column in the same solvent. On developing with benzene, no separation was observed, a reddish-orange band passing quickly through the column without being adsorbed. The solid was therefore recovered and submitted to a further chromatogram using a 50% benzene-light petroleum (60-80°) mixture as solvent. This time, a separation was

obtained. A light orange band passed slowly through the column and was collected as a light orange solution with a green fluorescence. On concentrating the volume of this solution, an orange solid was obtained, m.p. 230°, identical with that isolated in the original fractional crystallisation. A reddish-orange band remained strongly adsorbed at the top of the column, which was therefore extruded, and the reddish-orange material eluted with hot benzene. On reducing the volume of the solution, a deep orange solid was obtained which sintered at 179° and melted at 181-2°. Further crystallisations from light petroleum (60-80°) gave deep orange needles, m.p. 180·5°, which analysed in agreement with its formulation as a dichlorobenzacridine. The isomers were obtained in approximately equal quantities.

The problem was now to identify which was the 5:6- and which the 5:8-isomer. On the basis of the melting points of related compounds, it was thought that the higher melting isomer (231-2°) might be the 5:8- and the lower melting isomer (180·5°), the 5:6-dichloro-2:3-benzacridine. Thus, Lehmstedt and Schrader (1937) obtained mixtures 5-chloro- 6·and 8-substituted acridones by the cyclization of 3^1-substituted diphenylamine carboxylic acids with phosphorus oxychloride.

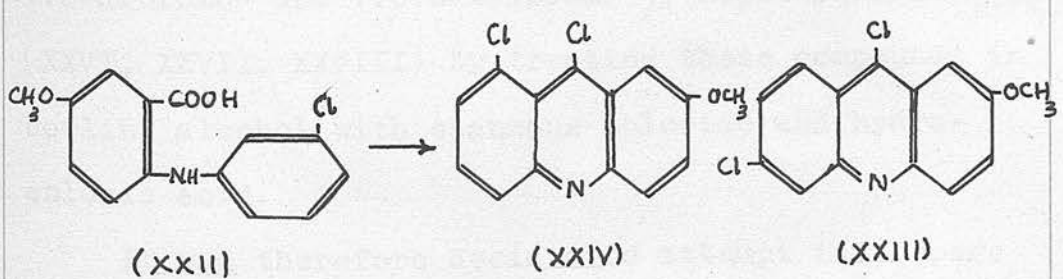


In every case, the compound with the lower melting point proved to be the 5-chloro-6-substituted isomer, and that with the higher melting point, the 5-chloro-8-substituted isomer. Similarly, Bradbury and Linell (1942) on cyclizing 2-(m-chloroanilino)-4-nitrobenzoic acid (XIX) obtained a mixture of 2-nitro-5:6-dichloro- (XX) and 2-nitro-5:8-dichloroacridine (XXI), the latter compound having the higher melting point. Both Lehmstedt and Schrader and Bradbury and Linell found that a preponderance of the 5:6-isomer, i.e. the compound with the lower melting point, was formed.



(XIX) (XX) (XXI)

However, Dauben (1948), on cyclizing 2-(m-chloroanilino)-5-methoxy benzoic acid (XXII) with phosphorus oxychloride isolated only one pure dichloro compound. He points out that Nargund (1946) claimed to have isolated a different dichloro compound as the sole product from the same reaction which he had identified as 3-methoxy-5:8-dichloroacridine (XXIII). The latter worker apparently published no experimental data and no physical properties for this compound. However, 3-methoxy-5:8-dichloroacridine is a well-known compound, having been prepared by Mauss and Mietzch during their synthesis of mepacrine. The melting point of this compound is 162°. As the product isolated by Dauben melted at 182° and depressed the melting point of 3-methoxy-5:8-dichloroacridine to 145-158°, he assumed it to be the 5:6-dichloro isomer (XXIV). Thus, in this instance the higher melting compound appears to be the 5:6-dichloro compound, and the lower melting compound the 5:8-dichloro compound, thus proving an exception to the general rule.



(XXII) (XXIV) (XXIII)

It was therefore a matter of considerable importance to decide which of the two compounds was the 5:6- and which the 5:8-dichloro isomer.

As already described, it was found in the benzquinoline and pyridoquinoline series that the bromine atom in 1-bromo-β-naphthylamine and 5-bromo-6-aminoquinoline were remarkably labile, so much so that in Skraup reactions carried out on these compounds, the major products were the angular 5:6-benzquinoline and p-phenanthroline, the bromine having been eliminated wholly or partially so that no 8-bromo-6:7-benzquinoline and very little 8-bromo-6:7:2^1:3^1-pyridoquinoline was formed. It was therefore thought that in 1-bromo-5:8-dichloro-2:3-benzacridine (XXV) where the bromine atom is situated in a position comparable with that in 1-bromo-β-naphthylamine and 5-bromo-6-aminoquinoline, the bromine might be labile and so might be reduced under acid conditions to yield 5:8-dichloro-2:3-benzacridine (XII). Reference may also be made to some observations by Franzen and Stäuble (1921) who eliminated the α-bromine from 1-bromo-, 1:6-dibromo- and 1:3:6-tribromo-β-naphthylamine (XXVI, XXVII, XXVIII) by treating these compounds in boiling alcohol with stannous chloride and hydrochloric acid.

It was therefore decided to attempt to prepare

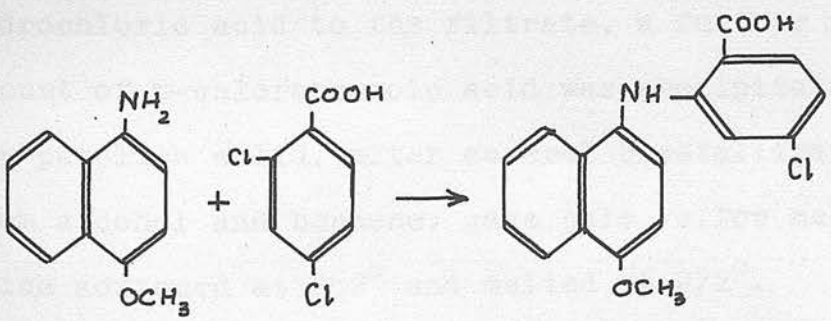
1-bromo-5:8-dichloro-2:3-benzacridine (XXV) by condensing 1-bromo-β-naphthylamine with 2:4-dichlorobenzoic acid, and ring-closing the resulting 4-chloro-2-(1¹-bromo-β-naphthylamino)-benzoic acid (XXIX) with phosphorus oxychloride. Accordingly a mixture of 1-bromo-β-naphthylamine and potassium 2:4-dichlorobenzoate was heated in an oil-bath at 150° for six hours, amyl alcohol being used as solvent and copper-bronze as catalyst. The solution at first became green and finally black. On cooling, a brownish solid separated which was filtered off, washed thoroughly with acetone and extracted with hot dilute sodium carbonate solution. The bulk of the material was insoluble and was filtered off. On acidifying the hot carbonate extract with acetic acid, no solid was formed, but on adding hydrochloric acid, a curdy white precipitate separated. This was filtered off and purified by re-extracting with sodium carbonate, acidifying the extract, and crystallising the resulting precipitate from dilute acetic acid, white needles being obtained, m.p. 241-3°. This compound gave a positive Beilstein reaction but contained no nitrogen. It was eventually identified as p-chlorobenzoic acid (XXX), a mixed melting point with an authentic specimen of this acid showing no depression. The formation of this compound is

discussed below.

The amyl alcohol filtrate and the acetone washings were now steam distilled. Towards the end of the distillation a pinkish solid, identified as unchanged 1-bromo-/3-naphthylamine, began to separate in the condenser. When the distillation was finished, the residual black oil was extracted with hot potassium carbonate solution. The oil did not appear to dissolve but formed an oily suspension, difficult to filter. On acidifying the hot filtrate with acetic acid, only a small quantity of an oily pinkish solid separated. This was filtered off and the filtrate acidified with hydrochloric acid, when a curdy white precipitate, identified as more p-chlorobenzoic acid, separated in quantity. The minute yield of the oily material precipitated by the acetic acid prevented further purification. A similar experiment in which the time of heating was reduced from six hours to two gave the same result. No improvement resulted from the addition of a trace of potassium iodide to the reaction mixture. It therefore appears that, instead of condensing with the amine, 2:4-dichlorobenzoic acid is being partially dechlorinated to give p-chlorobenzoic acid.

This observation is analogous to certain findings by Goldberg and Kelly (1946), who, on carrying

out various Ullmann condensations using 2-chloro-4-nitrobenzoic acid, found that in certain cases p-nitrobenzoic acid was formed in considerable quantity. Bachmann and Wetzel (1946) have also reported that when 2:4-dichlorobenzoic acid is condensed with 4-methoxy-α-naphthylamine hydrochloride (XXXI), a white product, m.p. 225-242°, can be isolated which is soluble in sodium bicarbonate, gives a positive halogen test and does not contain nitrogen. These workers failed to identify this material, but in the light of the results already described for the condensation of 1-bromo-β-naphthylamine with 2:4-dichlorobenzoic acid, it is possible that this white product was impure p-chlorobenzoic acid.



(XXXI)

Goldberg and Kelly also found that if isopropyl alcohol was substituted for amyl alcohol as solvent,

the condensations took place with a good yield of the phenyl anthranilic acid derivatives. The condensation was therefore repeated using iso-propyl alcohol as solvent. The reaction mixture again became green in colour, but no blackening was observed. On cooling, the greenish solid which separated was filtered, washed thoroughly with acetone, extracted with sodium carbonate, and the extract acidified with hydrochloric acid. Only a small quantity of a curdy white precipitate, identified as p-chlorobenzoic acid, was obtained. The isopropyl alcohol filtrate and acetone washings were steam distilled, some unchanged 1-bromo-β-naphthylamine coming over with the steam. The thick oil which remained in the flask was thoroughly extracted with hot potassium carbonate solution, and the extract acidified with acetic acid. A purplish solid separated and was filtered off. On adding hydrochloric acid to the filtrate, a further small amount of p-chlorobenzoic acid was precipitated. The purplish solid, after several crystallisations from alcohol and benzene, gave pale yellow needles which softened at 262° and melted at 272°. This material gave analytical figures agreeing with those calculated for 4-chloro-2-(1'-bromo-β-naphthylamino) benzoic acid (XXIX). The yield obtained, however, was still extremely poor, the bulk of the material

remaining as a black oil, insoluble in potassium carbonate. It was therefore decided to attempt to prepare the same compound by a different method.

On adding bromine, dissolved in glacial acetic acid, to N-acetyl-β-naphthylamine in the same solvent, 1-bromo-N-acetyl-β naphthylamine is obtained in good yield. It was hoped that on adding bromine to 4-chloro-2-(β-naphthylamino)-benzoic acid (XXXII) under the same conditions, the bromine would enter the one position and give 4-chloro-2(1^1-bromo-β-naphthylamino)-benzoic acid (XXIX). This did indeed prove to be the case. 4-chloro-2-(β-naphthylamino) benzoic acid (XXXII) was prepared as described by Dobson, Hutchison and Kermack (1948). A mixture of β-naphthylamine, potassium 2:4-dichlorobenzoate, amyl alcohol and copper bronze was refluxed in an oil bath at 150° for six hours. The mixture became dark-purple in colour, and on cooling a dark-purple oily solid separated. This was filtered off and washed thoroughly with acetone. All the purple material dissolved in the acetone and only a small amount of a greenish white solid remained, which on extraction with hot alkali and acidification, yielded only a small quantity of a white solid, identified as p-chlorobenzoic acid. This result is in direct contrast to that obtained by Dobson, Hutchison and

Kermack who recorded a yield of approximately 75% of 4-chloro-2-(β-naphthylamino)-benzoic acid at this point, and who did not isolate any p-chlorobenzoic acid. The difference may lie in the extent to which the purple solid was washed with acetone; in the present experiment, a considerable quantity of acetone was used to dissolve out all the purple material which contains the desired acid. If the former workers only washed superficially at this point, the naphthylanthranilic acid would remain in the solid and the small quantity of p-chlorobenzoic acid could easily be missed.

The amyl alcohol filtrate and acetone washings were now steam distilled. Some β-naphthylamine passed over in the steam, leaving a black tarry residue in the flask. This was extracted thoroughly with hot dilute ammonium hydroxide, a considerable portion being insoluble. On extracting the insoluble material with dilute hydrochloric acid and making the extract alkaline with caustic soda, a pinkish solid was obtained which was identified as some unchanged β-naphthylamine. The hot ammonia solution from the first extraction, on acidifying with acetic acid, yielded a purplish precipitate which, on recrystallising from alcohol, yielded purplish crystals. On further recrystallising from benzene, however, pale

yellow needles were obtained, m.p. 231-2°, which was concluded to be 4-chloro-2-(β-naphthylamino) benzoic acid. In their paper, Dobson, Hutchison and Kermack describe this compound as pale violet needles from alcohol, m.p. 272° - this melting point is a typographical error for 227°.

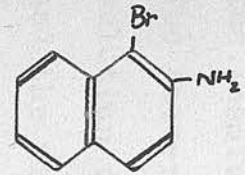
For purposes of comparison with the Ullmann condensation already described on 1-bromo-β-naphthylamine and 2:4-dichlorobenzoic acid, the experiment was repeated using isopropyl alcohol as solvent in place of amyl alcohol. No condensation took place, however, the reactants being recovered unchanged. This experiment was carried out like the other experiments without a trace of potassium iodide; it is possible that isopropyl alcohol with potassium iodide might be effective, but this has not yet been tried.

4-chloro-2-(β-naphthylamino)-benzoic acid was now dissolved in cold, glacial acetic acid and the calculated amount of bromine in the same solvent was slowly added with stirring. After a few minutes, a pale yellow solid began to separate. The mixture was allowed to stand for half-an-hour, then the precipitate was filtered off and crystallised several times from alcohol. Pale yellow, rectangular plates were obtained which softened at 262° and melted at 272°, and which did not depress the melting point of

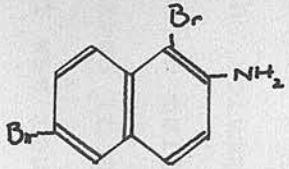
a specimen of 4-chloro-2-(1^1-bromo-β-naphthylamino)-benzoic acid (XXIX) obtained as described previously by an Ullmann condensation of 1-bromo-β-naphthylamine and 2:4-dichlorobenzoic acid. In a similar experiment carried out on a larger scale, the acetic acid solution was warmed to dissolve the 4-chloro-2-(β-naphthylamino)-benzoic acid more easily, and the reactants were then mixed while the solution was still warm. This time, a bright yellow solid was obtained which after several crystallisations from alcohol melted at 278°. This compound gave the following analytical results -

Found: C - 47.1; H - 2.6; N - 3.1.

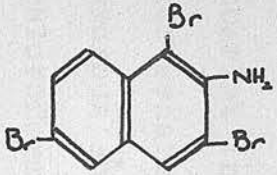
Percentage values calculated for 4-chloro-2-(1^1-bromo-β-naphthylamino) benzoic acid are - C - 54.2, H - 2.9, N - 3.7, and those for 4-chloro-2-(1^1:x^1-dibromo-β-naphthylamino) benzoic acid - C - 44.8, H - 2.2, N - 3.1. These figures suggest that this material may be a mixture of a mono-bromo and a dibromo compound. This is not unlikely as Franzen and Stäuble report the formation of 1:6-dibromo- and 1:3:6-tribromo-β-naphthylamine on adding the calculated quantities of bromine to N-acetyl-β-naphthylamine and hydrolysing the products. The dibromo compound may thus be 4-chloro-2-(1^1:6^1-dibromo-β-naphthylamino) benzoic acid (XXXIII).



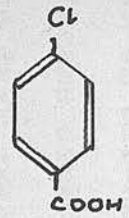
(XXVI)



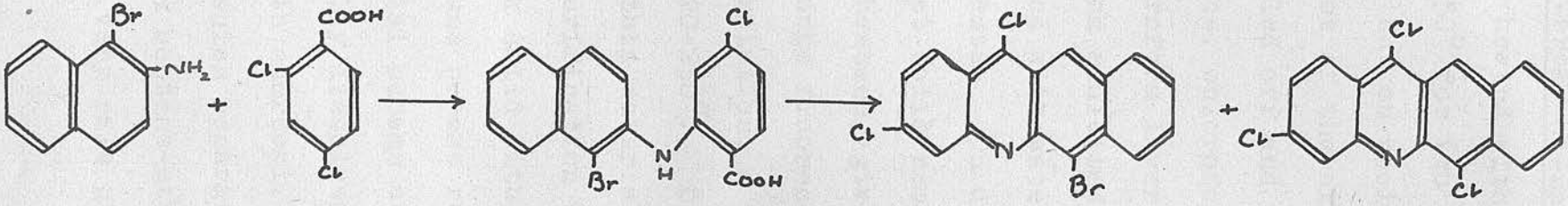
(XXVII)



(XXVIII)



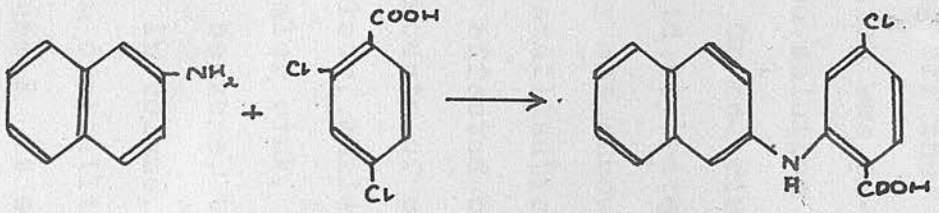
(XXX)



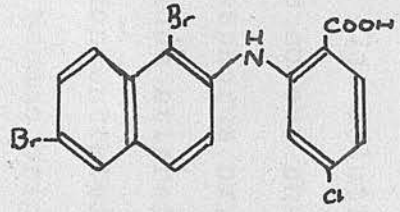
(XXIX)

(XXV)

(XXXV)



(XXXII)



(XXXIII)

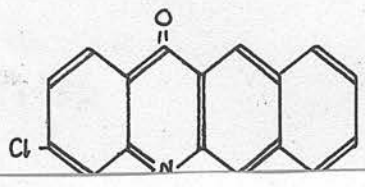
4-chloro-2-(1'-bromo-β-naphthylamino) benzoic acid (XXIX) was now heated with phosphorus oxychloride in an oil-bath at 150° for two hours. The solution became dark purple, but on cooling, the colour changed to dark green. Most of the excess phosphorus oxychloride was distilled off and the residue stirred into a mixture of ice, chloroform and concentrated ammonia. The chloroform layer, which became bright scarlet in colour and exhibited a green fluorescence, was separated, washed with water and dried over anhydrous sodium sulphate. On distilling off the chloroform, a scarlet solid remained which was extremely soluble in benzene, giving a red solution with a brilliant orange fluorescence. On reducing the volume of this solution, a pink solid separated which melted from 220-230°. Difficulty was encountered in purifying this material by crystallisation. It was found that purification was best effected by triturating the pink solid with small amounts of cold benzene. The benzene became red in colour, while the insoluble material became an even paler pink. The latter was finally dissolved in hot benzene, the solution treated with charcoal, reduced in volume, and the pink solid which separated again crystallised several times from a benzene-ether mixture. It was finally obtained as very pale pink needles m.p. 241-2°

which gave analytical figures agreeing with its formulation as 1-bromo-5:8-dichloro-2:3-benzacridine (XXV). This was the major product of the reaction. On heating this solid on the water-bath with dilute acid, a yellowish solid was formed which melted over 360° and which analysed in accordance with its formulation as 1-bromo-8-chloro-2:3-benzacridone (XXXIV).

The benzene from the deep red mother liquors was now evaporated leaving a deep red solid melting from approximately 170-190°. On extracting a portion of this solid with alcohol, a red, fluorescent solution was obtained, but after boiling this solution for a few minutes, the red colour was discharged, and a yellow solution with a brilliant green fluorescence was formed. The same result was obtained on adding charcoal to a cold alcohol solution of the red solid. On reducing the volume of the yellow alcohol solution, a yellow solid separated, which after several crystallisations melted at 349-50°. This compound analysed as follows:-

Found: C - 64.1; H - 2.6; N - 4.3.

This is obviously not a bromo-chloro acridone which has a percentage composition of C - 56.9; H - 2.5; N - 3.9. However, the figures calculated for a dichlorobenzacridone are C - 64.95, H - 2.85, N - 4.5. Although the carbon is rather high, these figures



(XXXIV)

are otherwise in good agreement with the analytical values obtained for the compound described above. It was thus thought that the dark-red compound might be a trichlorobenzacridine. Several crystallisations from benzene did not appear to purify this compound, so it was decided to chromatograph this material. The red solid was dissolved in benzene and passed into an alumina column in the same solvent. No separation was observed, however, a red band passing quickly through the column giving a red solution, which, on evaporation, yielded the original material. A second chromatogram was carried out using a 50% benzene-light petroleum mixture as solvent. This time, some separation was effected. A red band passed quickly down the column leaving a yellow band adsorbed on the alumina. Ten 100 c.c. portions were collected, and the volumes of the various fractions reduced to about 10 c.c. The first two fractions gave yellow-orange solutions with a green fluorescence. On standing, however, deep-red, rod-shaped crystals separated, which after several crystallisations from light petroleum melted at 264-5°. This material gave a nitrogen value of 4.3%. That calculated for a trichloro-benzacridine is 4.2% and for a bromochlorobenzacridine 3.7%. It thus appeared that the red compound was a trichlorobenzacridine. The

formation from it of the dichloro-acridone, already described, on recrystallisation from alcohol is readily understood, the hydrolysis of the chlorine atom in the five position being easily effected by the trace of water present in the alcohol. This replacement of a chlorine atom in the five position, especially in pyridoacridines, by alcohol containing only traces of water, has been observed by Dobson, Hutchison and Kermack. The other eight fractions from the chromatogram gave first a mixture of pink and red material, then some pure pink solid, identified as 1-bromo-5:8-dichloro-2:3-benzacridine, and finally a yellow, high-melting solid, probably acridone, which was not completely purified.

It would thus seem that in addition to the expected 1-bromo-5:8-dichloro-2:3-benzacridine (XXV), a trichloro-benzacridine is also formed to a slight extent during the reaction. Two of these chlorine atoms are situated at positions five and eight. As the other chlorine atom appears with the simultaneous disappearance of the bromine atom, it seemed highly probable that the third chlorine atom would be in position one, having replaced the bromine atom in this position, thus forming 1:5:8-trichloro-2:3-benzacridine (XXXV). That this hypothesis is correct will be demonstrated later in this thesis.

This replacement of bromine by chlorine appears to be a somewhat unexpected reaction, but some previous work in this laboratory (unpublished) suggested that some such reaction may occasionally take place. Thus Hutchison, in his Ph.D. thesis (1946), reported that on attempting to cyclize 5-chloro-(8^1-bromo-6^1-quinolyl) anthranilic acid (XXXVI), prepared by an Ullmann condensation on 8-bromo-6-aminoquinoline (XXXVII) and 2:4-dichlorobenzoic acid, with phosphorus oxychloride, a compound was obtained which gave analytical figures suggesting that a mixture of 2-bromo-5:7-dichloro- (XXXVIII) and 2:5:7-trichloro-3:4:2^1:3^1-pyridoacridine (XXXIX) had been formed. The only explanation appeared to be that the bromine atom was being partially replaced by a chlorine atom. We have ourselves carried out some experiments with the object of confirming Hutchison's results. In order to simplify matters, it was decided to use o-chlorobenzoic acid instead of 2:4-dichlorobenzoic acid. Thus 8-bromo-6-aminoquinoline was condensed with o-chlorobenzoic acid, and the resulting (8^1-bromo-6^1-quinolyl)-anthranilic acid (XL) refluxed with phosphorus oxychloride for eight and then for twenty-four hours. The products isolated on working up these experiments by a method similar to that used by Hutchison, gave analytical figures suggesting in the

case of the eight hour experiment, that an 80-20% mixture of 2-bromo-5-chloro- (XLI) and 2:5-dichloro-3:4:2^1:3^1-pyridoacridine (XLII) had been formed, and in the case of the twenty-four hour experiment that an 80% conversion to the 2:5-dichloro compound had taken place.

Found: (1) eight-hour experiment -
C - 57.8, H - 2.85, Halides ≡ 1 mg. - 0.939

(2) twenty-four hour experiment -
C - 62.55, H - 2.4, Cl - 22.75

$C_{16}H_8N_2ClBr$ requires - C - 55.9
H - 2.33
Halides ≡ 1 mg. - 0.965.

$C_{16}H_8N_2Cl_3$ requires - C - 64.2
H - 2.67
Halides ≡ 0.960
(Cl - 23.75)

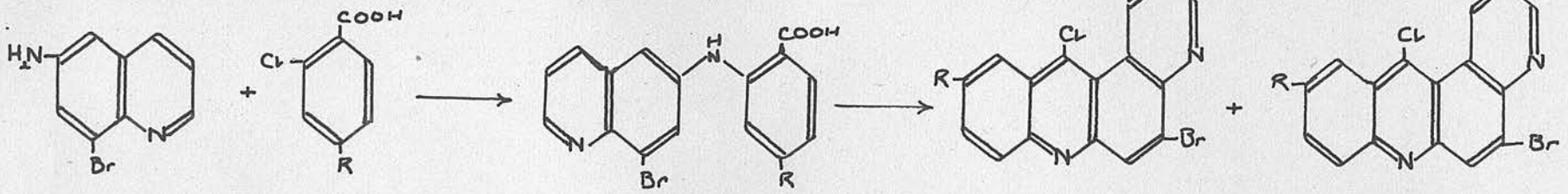
Furthermore, when this last compound was treated in phenol with diethylaminoethylamine, the product gave analytical figures agreeing closely with those calculated for 2-chloro-5-(diethylaminoethylamino)-3:4:2^1:3^1-pyridoacridine (XLIII) containing a trace of water.

Found: C - 68.35; H - 5.9; N - 14.6.

$C_{22}H_{23}N_4Br$ requires C - 62.4, H - 5.4, N - 13.2

$C_{22}H_{23}N_4Cl$ requires C - 69.75, H - 6.1, N - 14.7

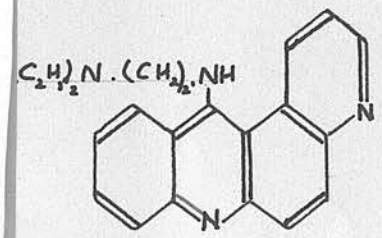
" " " ,$\frac{1}{2}H_2O$ requires C - 68.1, H - 6.2, N - 14.5.



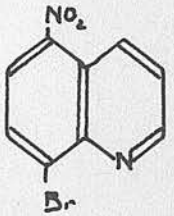
(XXXVII) (R = Cl)
(XL) (R = H)

(XXXVIII) (R = Cl)
(XLI) (R = H)

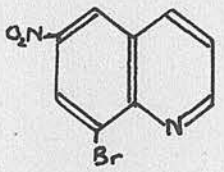
(XXXIX) (R = Cl)
(XLII) (R = H)



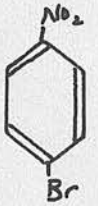
(XLIII)



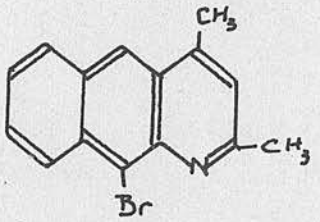
(XLIV)



(XLV)



(XLVI)



(XLVII)

It will be observed that in these pyridoacridines and in 1-bromo-5:8-dichloro-2:3-benzacridine (XXV), the bromine atoms are situated in similar positions with respect to a ring nitrogen, so that it is not altogether surprising that they react in a similar manner.

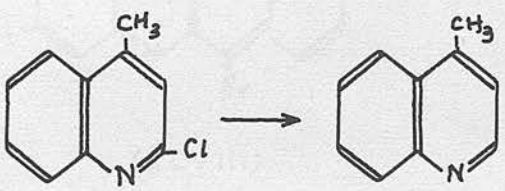
Nevertheless it is perhaps surprising that this type of replacement of bromine by chlorine takes place at all. A number of experiments were carried out to see if analogous results could be obtained with simpler compounds. Thus 5-nitro-8-bromoquinoline (XLIV), 6-nitro-8-bromoquinoline (XLV) and p-bromonitrobenzene (XLVI) were refluxed with phosphorus oxychloride for twenty-four hours but in no case was any replacement observed, the original compound always being recovered. The same result was observed with 8-bromo-2:4-dimethyl-6:7-benzquinoline (XLV) which resembles the bromobenzacridine quite closely, though here, the mixture was only refluxed for three hours. However, Kern (1907) found that by heating 5-bromo-6-aminoquinoline in a sealed tube with concentrated hydrochloric acid, it was converted to 5-chloro-6-aminoquinoline, thus providing evidence in favour of the above replacement.

Returning now to 1-bromo-5:8-dichloro-2:3-benzacridine (XXV), we have to discuss the attempts which were made to remove the bromine atom from position

one. Following the method outlined by Franzen and Stäuble for the removal of bromine from 1-bromo-β-naphthylamine, a mixture of 1-bromo-5:8-dichloro-2:3-benzacridine, stannous chloride, concentrated hydrochloric acid and alcohol was heated on the water-bath for five hours. After a few minutes, the pink colour of the acridine was changed to the buff colour of the corresponding acridone, but no further change was observed. The mixture was poured into water, the buff solid filtered off and recrystallised from alcohol as needles m.p. $>360^{\circ}$. The alcohol had only a very faint fluorescence. Now, one of the outstanding physical differences between 1-bromo-8-chloro-2:3-benzacridone on the one hand, and the 6- and 8-chloro-2:3-benzacridones on the other, is that the latter exhibit a brilliant green fluorescence, while the former shows only a very faint fluorescence in alcohol. As no brilliant fluorescence was obtained in this experiment, it was concluded that the bromine atom had not been removed. This was confirmed, as the solid obtained did not depress the melting point of an authentic specimen of 1-bromo-8-chloro-2:3-benzacridone.

As it was thought that the reaction might be more successful if the acridone was kept in solution throughout, the experiment was repeated using a much

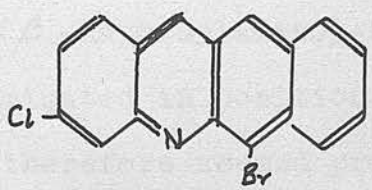
larger volume of alcohol. Again, however, no fluorescence was produced, the original bromo-acridone being recovered. A further experiment was also carried out using glacial acetic acid as solvent, but again no reduction was effected. It was therefore decided to employ much more drastic conditions, and so a mixture of phosphorus and hydriodic acid was used as reducing agent. This method had been used successfully by Knorr (1886) to remove chlorine from α-chloro-lepidine (XLVII).



(XLVII)

Accordingly, a mixture of 1-bromo-8-chloro-2:3-benzacridone, red phosphorus and hydriodic acid was heated on the water-bath for three hours, and then poured into water. The dark-red solid was filtered, washed and thoroughly extracted with alcohol, the material from this solution being finally obtained as a pale yellow solid m.p. 212-213°, which analysed as follows:

C - 58.8, H - 2.6. The low melting point of this compound and the ease with which it dissolved in alcohol, benzene and dilute acids suggested that the acridone had been reduced to an acridine. The low carbon and hydrogen values obtained on analysis also indicated that the bromine atom had not been removed, but that the compound obtained might be a slightly impure specimen of 1-bromo-8-chloro-2:3-benzacridine (XLVIII) which contains C - 59.6% and H - 2.6%.



(XLVIII)

It therefore appeared that the only reduction which had been effected was that of the acridone to the acridine, the bromine atom remaining quite stable under the experimental conditions employed. The experiment was repeated, a trace of copper bronze being included in the reaction mixture, but the same result was obtained, the bromine atom being unaffected, and a compound identical with that obtained in the

previous experiment being isolated. The alcohol extract in this experiment did at first show a green fluorescence, which, however, disappeared on treating the solution with charcoal. The bromine atom may thus have been removed to a very slight extent.

It was concluded from these experiments that the bromine atom in 1-bromo-8-chloro-2:3-benzacridone was more stable than might be expected from comparison with related compounds. It was now decided to reverse the procedure and to try to obtain 1-bromo-5:8-dichloro-2:3-benzacridine by brominating 5:8-dichloro-2:3-benzacridine. It has already been shown that 4-chloro-2-(β-naphthylamino)-benzoic acid could be readily brominated in position one of the naphthalene ring. It therefore seemed probable that, if bromine did attack 5:8-dichloro-2:3-benzacridine, it would do so in the one position. The actual bromination experiments were carried out on the acridone. Thus whichever of the acridones, obtained on hydrolysis of the benzacridines formed by the ring-closure of 3-(m-chloroanilino)-2-naphthoic acid, yielded a compound identical with 1-bromo-8-chloro-2:3-benzacridone would be the 5:8-dichloro isomer.

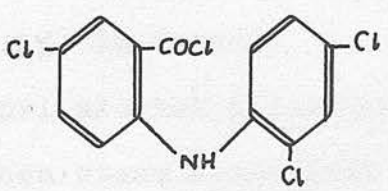
Various experiments were carried out using the higher melting isomer (231-2°) which was considered most probably to be the 5:8-isomer. The bromination

was carried out first in glacial acetic acid, then in nitrobenzene, a trace of iodine being added as catalyst, but none of the desired bromo-acridone was isolated. As both 6-chloro- and 8-chloro-2:3-benzacridone, and the desired 1-bromo-8-chloro-2:3-benzacridone have very high melting points, the main indication that bromination had taken place would be the disappearance of the bright fluorescence in alcohol and the purple colour in concentrated sulphuric acid. Thus if the bromoacridine were only partially formed, it would be difficult to detect. The products from the present experiments fluoresced brightly in alcohol and gave a deep-purple colour in concentrated sulphuric acid, and so it was concluded that bromination had not taken place.

Meanwhile, however, another line of attack for the identification of the isomers had been suggested. In a repeat experiment on the ring-closure of 3-(m-chloroanilino)-2-naphthoic acid with phosphorus oxychloride, some phosphorus pentachloride was added to the reaction mixture, as it was thought that the addition might increase the yield of the isomeric dichlorobenzacridines. On pouring the residue, after the removal of the excess phosphorus oxychloride, into the usual ice, ammonia, chloroform mixture, a deep-red colour was produced in the chloroform layer

in contrast to the orange colouration obtained in previous experiments. This layer was separated, washed, dried and the solvent removed. The deep red solid which was left was dissolved in a 50% benzene-light petroleum mixture and passed into an alumina column in the same solvent. A deep red band passed very quickly through the column, being collected as an orange solution, and was followed more slowly by a light orange band, while a deep reddish-orange band remained adsorbed at the top of the column. On evaporating the solvent from the first few fractions, a deep red solid m.p. 262° crystallised which did not depress the melting point of the deep-red compound obtained as a by-product in the ring-closure of 4-chloro-2-(1¹-bromo-β-naphthylamino)-benzoic acid, which, as already mentioned, has been identified as 1:5:8-trichloro-2:3-benzacridine. It therefore appeared that the phosphorus pentachloride was acting as a chlorinating agent, and that a chlorine atom was being introduced into the one position of the acridine nucleus. A similar chlorination was also observed when some 7-chloro-2:3-benzacridone, formed during the ring closure of 3-(p-chloroanilino)-2-naphthoic acid, in an experiment where insufficient ice was used while decomposing the excess phosphorus oxychloride, was treated with a mixture of phosphorus

pentachloride and phosphorus oxychloride in an attempt to convert it to the corresponding 5:7-dichloro-2:3-benzacridone. None of this compound was obtained, however, but a deep-red crystalline solid m.p. 259-260° was isolated which analysed in accordance with its formulation as a trichlorobenzacridine. Chlorination had obviously been effected. A somewhat similar example of a direct nuclear chlorination has been found by Goodall and Kermack (1936) who, on treating 2:4-dichloro-diphenylamine-2^1-carboxylic acid with phosphorous pentachloride, using chlorobenzene as solvent, obtained not the expected ring-closed 5-chloro-acridine, but a chlorinated product - 2:4:4^1-trichlorodiphenylamine-2^1-carboxylic acid chloride (XLIX).



(XLIX)

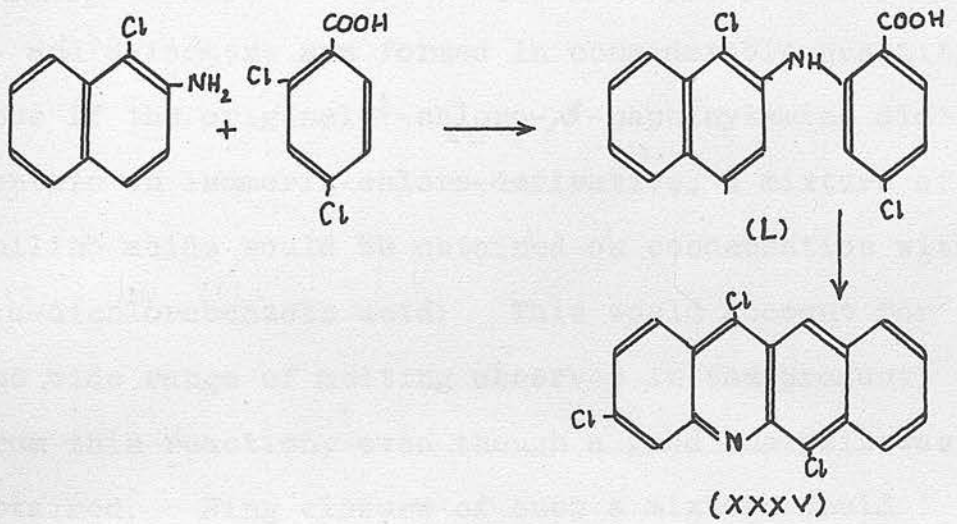
The light orange band from the chromatogram proved to be some of the higher melting dichloro-isomer, and the reddish-orange band some of the lower melting isomer.

It might be suitable at this point to discuss the preparation of an unambiguous specimen of 1:5:8-trichloro-2:3-benzacridine (XXXV). Thus a mixture of 1-chloro-β-naphthylamine, 2:4-dichlorobenzoic acid, anhydrous potassium carbonate, with traces of copper bronze and potassium iodide as catalysts, was refluxed in an oil-bath at 130° for six hours, iso-propyl alcohol being used as solvent. The whitish solid which separated on cooling was filtered, washed with acetone and extracted with hot dilute ammonium hydroxide. On making the extract acid with hydrochloric acid, a considerable amount of a white solid was precipitated which was identified as p-chlorobenzoic acid. This result is similar to that obtained on carrying on an Ullmann condensation on 1-bromo-β-naphthylamine, which has already been described (see p. 124) in detail.

The isopropyl alcohol filtrate and the acetone washings were then steam distilled, some unchanged 1-chloro-β-naphthylamine coming over in the steam. A black, oily residue was left, which on extracting with dilute hydrochloric acid and basifying the

extract, yielded more unchanged 1-chloro-β-naphthylamine. The residue, insoluble in acid, was then extracted with dilute ammonia, and the hot extract acidified with acetic acid. A yellowish solid was precipitated, which crystallised from aqueous alcohol as rectangular tetrahedra, and from benzene as long needles, which softened at 230° and melted at 255°. After drying over phosphorus pentoxide for three hours, the melting point changed to 235-245°. However, the analytical figures for this compound agreed closely with those calculated for 4-chloro-2-(1'-chloro-β-naphthylamino)-benzoic acid (L), and so it was thought to be pure. It was now cyclized by heating with phosphorus oxychloride for two hours in an oil-bath at 180°, the reddish-brown oily product being worked up in usual way. The chloroform became deep-red in colour, and a green fluorescence was observed. On removing the solvent, a deep-red solid was obtained, which was chromatographed using alumina as adsorbent, and a 50% benzene-light petroleum (60-80°) mixture as solvent. A deep red band passed quickly through the column, giving an orange fluorescent solution and leaving a yellow band adsorbed on the alumina. On evaporating the solvent from the first washings, a deep red solid crystallised which was finally obtained as long, red rod-shaped crystals

m.p. 262-3°. This compound analysed in accordance with its formulation as 1:5:8-trichloro-2:3-benzacridine (XXXV), and did not depress the melting points of the compounds already described, which were obtained as by-products in the cyclization of 4-chloro-2-(1¹-bromo-β-naphthylamino)-benzoic acid (XXIX) with phosphorus oxychloride and of 3-(m-chloroanilino)-2-naphthoic acid (XV), using a mixture of phosphorus oxychloride and of phosphorus pentachloride.



The yellow band which remained adsorbed on the column was eluted with benzene, giving a yellow, non-fluorescent solution. On evaporation, a small quantity of a pinkish-orange solid was obtained, which on purification melted at 238°. This compound analysed as follows:-

Found: C - 59.7; H - 2.3.

$C_{17}H_8NCl_3,\frac{1}{2}H_2O$ requires C - 59.7, H - 2.6.

This compound therefore appeared to be a trichloro benzacridine, isomeric with deep-red 1:5:8-trichloro-2:3-benzacridine. It may be that in the preparation of 1-chloro-β-naphthylamine by bubbling chlorine through an acetic acid solution of N-acetyl-β-naphthylamine, and hydrolysing the product, a small quantity of an isomeric chloro-compound was formed. This is not unlikely, as in the nitration of N-acetyl-β-naphthylamine, besides 1-nitro-β-naphthylamine, the 5- and 8-isomers are formed in considerable quantity. Thus if the original 1-chloro-β-naphthylamine did contain an isomeric chloro-derivative, a mixture of anilino acids would be obtained on condensation with 2:4-dichlorobenzoic acid. This would account for the wide range of melting observed in the product from this reaction, even though a good analysis was obtained. Ring closure of such a mixture would naturally produce two isomeric compounds.

The characterisation of the deep-red compound, isolated from the ring-closure of 3-(m-chloroanilino)-2-naphthoic using a mixture of phosphorus oxychloride and phosphorus pentachloride, as 1:5:8-trichloro-2:3-benzacridine, thus suggested a method of identifying which of the dichloro compounds obtained in this experiment was the 5:8-dichloro isomer. The separate

isomers were dissolved in phosphorus oxychloride, various amounts of phosphorus pentachloride added, and the mixture refluxed in an oil-bath at 150° for two hours. The products were then worked up in a manner similar to that described for the usual ring-closure experiments with phosphorus oxychloride. The amount of phosphorus pentachloride used appears to be a critical factor in determining the products of these experiments. Unfortunately, the quantity used in the experiment referred to above involving the formation of 1:5:8-trichlorobenzacridine was not measured, so that the conditions used then could not be duplicated.

In the case of the higher melting isomer (m.p. 231-2°), three experiments were carried out using one, two and three moles of phosphorus pentachloride respectively. In the first of these experiments, no chlorination appeared to take place. The oxychloride, pentachloride, acridine mixture remained purple throughout, and on pouring into the ice, ammonia, chloroform mixture the orange colour of the original compound was observed. The base was recovered quantitatively on working up the experiment. However, when two molecules of phosphorus pentachloride were employed, the chloroform layer remained almost colourless and a pink solid was obtained.

After crystallising several times, this material was obtained as pink, rectangular tetrahedra, which turned a very deep red colour at 175-180°, melted sharply at 183° and which analysed as follows -

Found: C - 50.15; H - 2.1; N - 3.4

$C_{17}H_6NCl_5$ requires C - 50.8, H - 1.5, N - 3.5.

$C_{17}H_8NCl_3Cl_2$ requires C - 50.55, H - 2.0, N - 3.5.

These figures suggest that this compound may be a pentachloro benzacridine which has been slightly hydrolysed to the acridone, but the observation that on heating, the pale pink colour is changed to deep-red, suggests that it may be a perchloride of a trichlorobenzacridine. The colour change on heating would then be explained by the extra molecule of chlorine attacking the trichlorobenzacridine and forming a pentachloro derivative. In the experiment using three molecules of phosphorus pentachloride, two fractions were obtained — a small amount of deep red solid which, on purification, melted at 185°, but which was insufficient for analysis, and a mixture of pale pink material which melted over a range of 30° (160-190°) and which was not purified further. The proximity of the melting point of the deep red compound obtained in this experiment (185°) and that of the pink compound (m.p. 183°) which turns deep-red before melting, obtained in the last experiment, may

not be without significance, if the perchloride hypothesis is correct. It may be that the red compound (m.p. 185°) is a pentachlorobenzacridine, possibly identical with that obtained on heating the perchloride of the corresponding trichlorobenzacridine (m.p. 183°), if such it is. In all these experiments, however, no trace of the dark-red 1:5:8-trichloro-2:3-benzacridine was found, which would identify the isomers, and so attention was turned towards the lower melting isomer (m.p. 180.5°).

In the first experiment with the lower melting isomer (180.5°), using one molecule of phosphorus pentachloride, a deep-orange red colour was produced in the chloroform layer. On working this experiment up as usual, two products were obtained, some of the original dichloro isomer, representing the bulk of the material, and a small amount of a rose-red solid, m.p. 240-44°, which was not purified further. This material did not depress the melting point of 1:5:8-trichloro-2:3-benzacridine, however, as on carrying out a micro melting point, deep-red crystals sublimed which had the long, rod-shaped appearance characteristic of the 1:5:8-trichloro compound. It was thought, therefore, that this rose-red material might be an impure specimen of 1:5:8-trichloro-2:3-benzacridine.

A second experiment was thus carried out using

two molecules of phosphorus pentachloride. This time a deep red solid was obtained, which after chromatographing using alumina as adsorbent and a 50% benzene-light petroleum (60-80°) mixture as solvent, melted at 240-44° and was identical with the material isolated in the last experiment. A second chromatogram was therefore carried out using pure light petroleum (60-80°) as solvent. No separation appeared to be effected, but the first two fractions collected yielded a small amount of deep-red, rod-shaped crystals, m.p. 262-3°, which did not depress the melting point of an authentic specimen of 1:5:8-trichloro-2:3-benzacridine, and which analysed in agreement with its formulation as a trichloro-benzacridine. The problem of the identification of the isomer was thus solved, the lower melting isomer (m.p. 180·5°) thus being 5:8-dichloro-2:3-benzacridine (XII), and the higher melting isomer (231-2°) being 5:6-dichloro-2:3-benzacridine (X). This result agrees with that found by Dauben (see p. 124), but is in contrast to the results generally obtained in other cases of ring-closure with m-substituted phenyl anthranilic acids, which have been discussed earlier in this thesis.

The later fractions collected in this chromatogram also yielded red solids, which were lighter in

colour, but which melted at lower temperatures and over a range. The last experiment using three molecules of phosphorus pentachloride threw some light on their constitution. This time two products were isolated — a small amount of red oil which could not be crystallised, and a very pale pink solid which melted to a deep red liquid at 205°. This compound analysed as follows -

Found: C - 50.05; H - 2.0; N - 3.2.

As in the corresponding experiment with the 5:6-isomer, this material may be a pentachloro derivative containing some water — ($C_{17}H_6NCl_5$, $\frac{1}{2}H_2O$ requires C - 49.7, H - 1.7, N - 3.4) — or it may be the perchloride of a trichlorobenzacridine — ($C_{17}H_8NCl_3.Cl_2$ requires C - 50.55, H - 2.0, N - 3.5). The difficulty experienced in obtaining the trichloro derivative pure, may thus have been due to the presence of higher halogenated products.

From the foregoing discussion, it will be seen that the four isomeric 5:6-, 5:7-, 5:8- and 5:9-dichloro-2:3-benzacridines have been prepared, and that the 5:8-, and thus the 5:6-, isomer has been identified by preparing from it, by treatment with phosphorus pentachloride, a trichloro benzacridine, identical with 1:5:8-trichloro-2:3-benzacridine obtained by an unambiguous route. In the course of the work

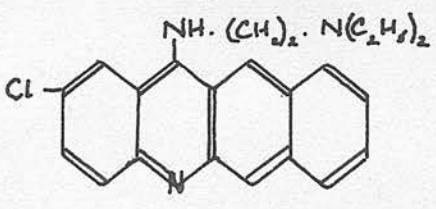
various other halogenated benzacridines were also obtained, and it is of interest to note the similarities and variations in their properties summarised in the following table.

2:3-benzacridine	M.p.	Colour	Fluorescence in benzene	Colour in concentrated sulphuric acid.
5:6-dichloro-	231-2°	light orange	green	purplish-blue
5:7-dichloro-	239-40°	red-orange	green	purplish-blue
5:8-dichloro-	180-5°	red-orange	green	purplish-blue
5:9-dichloro-	203°	orange-red	green	purple-red
x:5:7-trichloro-	259-60°	deep red	greenish-yellow	blue
1:5:8-trichloro-	264-5°	deep red	orange	blue
x:5:8-trichloro-	238°	pale pink	none	greenish-yellow
x:y:z:5:6-pentachloro- (or x:5:6-trichloroperchloride)	183°	pale pink	none	blue
x:y:z:5:8-pentachloro- (or x:5:8-trichloroperchloride)	205°	pale pink	none	green
1-bromo-5:8-dichloro-	241-2°	pale pink	none	pale yellow

The most striking difference is probably that between 1-bromo-5:8-dichloro- and 1:5:8-trichloro-2:3-benzacridine, colour, fluorescence and colour in sulphuric acid presenting a direct contrast, which is also

observed between the corresponding acridones.

Various attempts have been made to replace the 5-chlorine atom of 5:6-, 5:7-, 5:8- and 5:9-dichloro-2:3-benzacridine by a basic side-chain by heating a mixture of the acridine and the amine, using phenol as solvent, but so far, only the experiment with the 5:7-isomer has met with any success. 7-Chloro-5-(diethylaminoethylamino)-2:3-benzacridine (LI) was obtained in poor yield as an oil, which was crystallised and analysed as the oxalate. Other attempts yielded small amounts of oily products, which gave derivatives difficult to purify, but the main products of the reactions were acridones, even though the phenol-amine mixtures were dried under reduced pressure for a number of hours before the addition of the dichloro base.



(LI)

III. EXPERIMENTAL.

N-acetyl-β-naphthylamine.

β-naphthylamine (100 g.) was added to acetic anhydride (76 c.c.) and the mixture was heated on the water-bath for one hour. The solution was then poured into a large volume of water, a copious white precipitate being formed. This was filtered, dried and recrystallised from 75% aqueous alcohol as colourless plates, m.p. 131-132°, yield 125 g. (95%).

1-nitro-β-naphthylamine.

(a) Nitration of N-acetyl-β-naphthylamine.
The method followed was that described in Organic Synthesis, Col., Vol. II, 1943, 438. 1-nitro-2-acetamido naphthalene was obtained as fine yellow needles, m.p. 122-125°, yield - 17 g. (45% of theory).

(b) Hydrolysis of 1-nitro-2-acetamido-naphthalene.

(Meldola, J.C.S. 1885, 47, 520.)

1-nitro-2-acetamido-naphthalene (20 g.) was mixed with a small quantity of water, and concentrated sulphuric acid was added until complete solution was effected. The solution was heated on the water-bath for one hour and then poured into water, a yellow solid being precipitated. This was filtered, washed, dried and recrystallised from aqueous alcohol as yellow needles, m.p. 122-123°, yield 12 g. (69% of theory).

Attempts to prepare 9-nitro-1-azanthracene.

(cf. E.P. 394416; Lellmann and Schmidt, Ber., 1887, 20, 1354.)

1-nitro-β-naphthylamine was subjected to Skraup reactions, using various modifications.

(a) A mixture of 1-nitro-β-naphthylamine (5 g.), 69% sulphuric acid (32 c.c.), glycerine (7.2 c.c.) and arsenic acid (7.9 c.c.) was refluxed for 3-4 hours until no unchanged amine could be detected. A great deal of tarring took place. The black oily solution was poured into water and left over night to allow the tar to settle. The aqueous suspension was then filtered and basified with 10 $\bar{N}$ sodium hydroxide. A dark brown solid separated, which was filtered, washed and thoroughly extracted with benzene. The bulk of the material was insoluble in the benzene. On distilling off the solvent, a brown oil remained, which solidified on scratching. Recrystallisation from light petroleum (40-60°) yielded a small quantity of pale-yellow needles, m.p. 84-87.5°. Further crystallisations from the same solvent raised the melting point to 93°. This mixture gave a negative Beilstein test and did not depress the melting point of a specimen of 5:6 benzquinoline prepared by a Skraup reaction on β-naphthylamine. The nitro group

had thus been eliminated and the angular compound formed.

(b) The experiment was repeated, ferrous sulphate being added in an attempt to reduce tarring, but the only product isolated was 5:6 benzquinoline.

(c) A further experiment was carried out adding both ferrous sulphate and boric acid, but the same result was obtained.

(d) In experiments using 50% and 60% sulphuric acid, little or no tarring occurred, but no reaction took place, the original 1-nitro-β-naphthylamine being recovered.

Attempts to prepare 4-(1^1-nitro-2^1-naphthylimino)-pentan-2-one.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

(a) A mixture of 1-nitro-β-naphthylamine (1 g.), acetyl acetone (1½ c.c.) and anhydrous calcium sulphate (1 g.) was heated on the water-bath for six hours. No change in appearance was observed. The mixture was extracted with alcohol and the solution reduced in volume. Pale yellow needles crystallised, m.p. 120-2°, identical with the original 1-nitro-β-naphthylamine.

(b) The experiment was repeated, the mixture being heated in an oil-bath at 130° for two days, but again the original amine was recovered.

(c) The amine was refluxed with excess acetyl acetone for fifteen hours in the presence of anhydrous calcium sulphate, and then extracted with alcohol. The alcohol was removed from the solution, and the excess acetyl acetone distilled off under reduced pressure on the water bath. A black tar remained. This was extracted with alcohol, the solution treated with charcoal, and the volume reduced. A small quantity of yellow needles m.p. 119-122° crystallised, identical with the original 1-nitro-β-naphthylamine.

On reducing the volume of the alcohol solution further, a dark-brown oil was obtained which failed to crystallise. The addition of ethereal solutions of oxalic and picric acids to a solution of this oil in ether also yielded oily products.

(d) A mixture of 1-nitro-β-naphthylamine, acetyl acetone and anhydrous calcium sulphate was heated on the water-bath for three days, a trace of iodine being added as catalyst, but on working up this experiment, the amine was again recovered unchanged.

Ethyl-β-(1¹-nitro-2¹-naphthylamino)-α-carbethoxy-acrylate.

(cf. Schofield and Simpson, J.C.S., 1946, 1034.)

1-nitro-β-naphthylamine (1 g.), ethoxy methylene malonate (1 c.c.) were heated on the water-bath under reduced pressure for two hours. Bubbles appeared immediately in the mixture, but no solidification took place. Further heating in an oil bath at 150-170° for half-an-hour did not make the fluid solidify. It was then cooled and the greyish mixture extracted with alcohol. A small amount of a bright yellow insoluble solid material was left, m.p. 231-232°. Several recrystallisations from acetone raised the m.p. to 235°, a specimen on analysis giving the following results -

Found: C - 62.2; H - 4.25; N - 10.7.

Calculated for $C_{26}H_{19}N_4O_7$ - C - 62.5
H - 3.8
N - 11.2

Calculated for $C_{28}H_{26}N_4O_8$ - C - 61.6
H - 4.75
N - 10.3.

The formulation of this compound as ethyl-β-[bis-(1¹-nitro-2¹-naphthylamino)]-α-carbethoxy-acrylate, or as α-(1¹-nitro-2¹-naphthylcarbamyl)-β-(1¹¹-nitro-2¹¹-naphthylamino)-acrylate, has been discussed

in an earlier section of this thesis.

The alcoholic extract when reduced in volume yielded an orange-yellowish material melting at approximately 105°. After several crystallisations from light petroleum b.p. 100-120°, the orange crystals softened at 121° and melted at 129°. The analytical values for this product were C - 60.15; H - 5.05; N - 8.1.

$C_{18}H_{18}O_6N_2$ requires C - 60.3; H - 5.0; N - 7.8. It therefore appears that the orange solid, m.p. 129°, is the desired ethyl-β-(1¹-nitro-2¹-naphthylamino)-α-carbethoxy-acrylate.

This compound is soluble in alcohol, acetone, ether, light petroleum, and dilute acid, but insoluble in alkali.

1-bromo-β-naphthylamine.

(cf. Lellmann and Schmidt, Ber., 1887, 20, 3154.)

N-acetyl-β-naphthylamine (5 g.) was dissolved in 50% acetic acid, and bromine (1.5 c.c.), dissolved in the same solvent, was slowly added with stirring. After standing for about an hour, the mixture was poured into water, when 1-bromo-N-acetyl-β-naphthylamine was precipitated. A purified specimen melted at 134-135°. This was filtered off, dissolved in the minimum amount of hot alcohol, an equal quantity of concentrated hydrochloric acid added, and the solution left on the water-bath until no more crystals formed. The crystalline mass was filtered off, dissolved in water, and the solution made alkaline with ammonia. The precipitate of 1-bromo-β-naphthylamine was filtered off and recrystallised from aqueous alcohol as colourless needles, m.p. 63°, yield, 5.4 g. (75% of theory).

Attempts to prepare 9-bromo-1-azanthracene.

(cf. Lellmann and Schmidt, Ber., 1887, 20, 3154.)

(a) 1-bromo-β-naphthylamine (5 g.), 69% sulphuric acid (31 c.c.), ferrous sulphate (2 g.), glycerine (7.2 c.c.) and arsenic acid (7.9 c.c.) were mixed and refluxed gently in a sand bath for three hours. The solution became deep purple in colour and then tarred. The mixture was then poured into water, filtered to remove the tar which precipitated, and the filtrate made alkaline with 10 N̄-sodium hydroxide. A greyish-green oily solid precipitated. This was filtered off and extracted with light petroleum (60-80°); from the extract pale yellow needles crystallised, m.p. approximately 90°, which gave a negative Beilstein reaction and did not depress an authentic specimen of 5:6 benzquinoline. The residual oil, insoluble in light petroleum, gave no further crystalline product.

(b) A mixture of 1-bromo-β-naphthylamine (5 g.), 69% sulphuric acid (37.5 c.c.), glycerol (5 c.c.), sodium-m-nitrobenzene-sulphonate (5 g.) and water (.6 c.c.) was refluxed until the test for a free amino group was negative (approximately half-an-hour). The solution became dark, and on pouring into water, less tar separated than in the previous experiment. The tar was filtered off and the filtrate made

alkaline with 10 $\bar{N}$-sodium hydroxide. A black oil separated with was extracted with light petroleum (60-80°), giving a yellow solution. On distilling off the solvent, a brown oil was left, which could not be crystallised. It was thus redissolved in light petroleum (60-80°) and passed through an alumina column 9" x ¾" in the same solvent. Three zones separated - (1) bright yellow, (2) pale yellow, (3) pink. The colourless washings which came through before the bands, on evaporation gave .75 g. of almost white material, m.p. approximately 90°, identical with an authentic specimen of 5:6 benzquinoline.

The washings from the bright yellow band on evaporation yielded a yellow oil in small amount. This oil was dissolved in ether and the oxalate formed by adding an ethereal solution of oxalic acid. On reforming the base a pale yellow oily solid was obtained which crystallised from light petroleum (40-60°) as needles, m.p. 100-124°. This material gave a positive Beilstein test, but the amount obtained was so small that further purification was not feasible. The two other bands both yielded small amounts of oily products which failed to crystallise.

4-(1^1-bromo-2^1-naphthylimino)-pentan-2-one.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

A mixture of 1-bromo-β-naphthylamine (20 g.), acetyl acetone (20 c.c.) and anhydrous calcium sulphate (20 g.) was heated at 50° for eight hours and then allowed to stand over night. A mass of large hexagonal crystals was formed. The mixture was extracted with alcohol and the volume of the solution reduced. A pale, flesh-coloured solid crystallised out, m.p. 120-124°. Further crystallisations from alcohol yielded rectangular tetrahedra, m.p. 122-123°. Yield - 25 g. (86% of theory).

(Found: C - 59.15; H - 4.45; N - 5.15.

$C_{15}H_{14}NOBr$ requires C - 59.2
H - 4.9
N - 4.9.)

An experiment in which the mixture was heated on the water-bath for four hours yielded a black oil from which the same material was obtained but in smaller yield. A good yield was also obtained by allowing the mixture containing the amine, acetyl acetone and anhydrous calcium sulphate to stand for two days at room temperature.

4-(1^1-bromo-2^1-naphthylimino)-pentan-2-one is very soluble in alcohol, ether and benzene.

9-bromo-2:4-dimethyl-1-azanthracene.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

4-(1^1-bromo-2^1-naphthylimino)-pentan-2-one (3 g.) was added with stirring to concentrated sulphuric acid (10 c.c.) chilled to 2° C, over a period of three minutes, the mixture being thoroughly stirred during the addition. The sulphuric acid became yellow and then darkened. The solution was heated at 60° C for two minutes and then poured on to ice. The aqueous solution was yellow in colour and on standing a bright yellow solid precipitated, probably the sulphate. On making the mixture alkaline with 10 $\bar{N}$ sodium hydroxide a pale yellow solid was obtained, which after several crystallisations from alcohol melted at 168-169°. Yield - 2½ g. (93% of theory).

(Found: C - 62.85; H - 4.25; N - 5.15; Br - 27.8

Calculated for $C_{15}H_{12}N\,Br$ — C - 62.9
H - 4.2
N - 4.9
Br - 28.0.)

9-bromo-2:4-dimethyl-1-azanthracene is soluble in alcohol, ether and acetone. It dissolves easily in dilute hydrochloric acid yielding a bright yellow solution, but with dilute nitric acid, the solid becomes bright yellow in colour and only dissolves with difficulty. It is insoluble in alkalis.

Ethyl-β-(1¹-bromo-2¹-naphthylamino)-α-carbethoxy-acrylate.

(cf. Schofield and Simpson, J.C.S., 1946, 1034.)

A mixture of 1-bromo-β-naphthylamine (2.04 g.) and ethoxy methylene malonate (2.1 c.c.) was heated on the water-bath under reduced pressure. The fluid mass became greyish-blue in colour and after two hours it solidified. Heating was continued for another hour. The yellowish solid was then cooled and recrystallised several times from alcohol, finally yielding white rods m.p. 123-125°. Yield - 3½ g. (97% of theory).

(Found: C - 55.0; H - 4.7; N - 3.6; Br - 20.45

$C_{18}H_{18}O_4NBr$ requires C - 55.1
H - 4.6
N - 3.6
Br - 20.4.)

Ethyl-β-(1¹-bromo-2¹-naphthylamino)-α-carbethoxy acrylate is very soluble in alcohol and acetone, but only dissolves with difficulty in hot ether and light petroleum.

Attempts to prepare 9-bromo-3-carbethoxy-1-azanthracene.

(cf. Schofield and Simpson, J.C.S., 1946, 1034.)

(a) Ethyl-β-(1¹-bromo-2¹-naphthylamino)-α-carbethoxy acrylate (1½ g.) was dropped into liquid paraffin (50 c.c.) at 150°. The solution became very dark and on cooling only a very small amount of oily material separated. All attempts to crystallise this oil were unsuccessful.

(b) Ethyl-β-(1¹-bromo-2¹-naphthylamino)-α-carbethoxy acrylate (½ g.) was dropped into boiling diphenyl (25 g.) and boiling was continued for ten minutes. On cooling, no solid product separated. The diphenyl was removed by steam distillation, leaving a dark brown residue, insoluble in ether and only partly soluble in alcohol. Evaporation of the alcohol gave a small quantity of oily solid which on crystallisation from aqueous alcohol separated out as a light brown gelatinous solid, m.p. 280-5°. The amount was too small for further purification.

1-chloro-β-naphthylamine.

(cf. Gerhardt and Hamilton, J.A.C.S., 1944, 66, 479.
Etienne, Compt. rend., 1944, 218, 841.)

N-acetyl-β-naphthylamine (15 g.) was dissolved in glacial acetic acid and chlorine, which had been prepared by the action of concentrated hydrochloric acid on potassium permanganate, washed with water and dried with concentrated sulphuric acid, was bubbled slowly through the stirred solution until there was an increase in weight of 5.7 g. A white crystalline precipitate was formed. This was separated, dissolved in warm alcohol (50 c.c.), concentrated hydrochloric acid (5 c.c.) added, and the mixture heated on the water-bath until the separation of the crystalline solid was complete. The solution was then made alkaline with ammonia. The amine, purplish in colour, was collected and crystallised several times from alcohol as needles, m.p. 56°, yield - 10.5 g. (70% of theory)

9-chloro-1-azanthracene.

(Étienne, Compt. rend. 1944, 218, 841.
Gerhardt and Hamilton, J.A.C.S., 1944, 66, 479.)

1-chloro-β-naphthylamine (5 g.), 69% sulphuric acid (31 c.c.), glycerine (7.2 c.c.), arsenic acid (7.9 c.c.) and ferrous sulphate (2 g.) were mixed and refluxed for two to three hours until a negative diazo test was obtained. The solution became very dark and on pouring into water a considerable amount of tarry material separated. This was filtered off and the filtrate made alkaline with 10 N-sodium hydroxide. A greenish solid precipitated which was filtered off, washed, dried and recrystallised from benzene, giving pale yellow needles, m.p. 139-140°, yield .5 g.

4-(1[1]-chloro-β-naphthylimino)-pentan-2-one.

(cf. Johnson and Mathews, J.C.S., 1944, 66, 210.)

A mixture of 1-chloro-β-naphthylamine (1 g.), acetyl acetone (1 c.c.) and anhydrous calcium sulphate (1 g.) was heated on the water-bath for four hours, and then allowed to stand overnight. The oily mass was extracted with alcohol, the solvent evaporated, and the yellow, oily residue extracted with hot, light petroleum (40-60°). On cooling, an oil separated which solidified on scratching. After several crystallisations from the same solvent, 4-(1[1]-chloro-β-naphthylimino)-pentan-2-one was obtained as white rods, m.p. 86-88°. Yield - 72% of theory. It analysed as follows -

Found: C — H — N - 5·2

$C_{15}H_{14}NClO$ requires C - 69.36
H - 5.4
N - 5·4

9-chloro-2:4-dimethyl-1-azanthracene.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

4-(1[1]-chloro-β-naphthylimino)-pentan-2-one (½ g.) was slowly added with stirring to concentrated sulphuric acid (2 c.c.) chilled to 2° C. The yellow solution was then heated at 60° C. for two minutes and poured on to ice, producing a yellow solution from which a yellow solid separated on standing. On making the mixture alkaline with 10 N. sodium hydroxide, a very pale yellow solid separated, which was filtered, dried and crystallised from light petroleum (60-80°) as very pale yellow hexagonal plates with bevelled edges, m.p. 167°, yield - 89% of theory. It analysed as follows -

Found: C - 75.0; H - 5.1

$C_{15}H_{12}NCl$ requires C - 74.5
H - 5.0

9-chloro-2:4-dimethyl-1-azanthracene dissolves in alcohol, giving a colourless, non-fluorescent solution, but in light petroleum, a bright purple fluorescence is produced.

6-nitro-quinoline.

(cf. E.P. 394416; F.B. I. G. Farbenindustrie, 727528.)

A mixture of p-nitraniline (50 g.), 69% sulphuric acid (438 c.c.), glycerin (120 c.c.) and arsenic acid (100 c.c.) was refluxed for one to two hours, until a negative diazo-reaction was obtained. The dark solution was then cooled and poured into its own volume of water, when a considerable amount of black tar separated. This was filtered off and the filtrate made alkaline with 10 $\bar{N}$ sodium hydroxide. A light brown solid was precipitated, which was washed with water till neutral, dried and recrystallised from alcohol as buff needles, m.p. 153-154°. Yield - 47 g. (75% of theory).

6-aminoquinoline.

(cf. Hamer, J.C.S., 1921, 1435.)

Stannous chloride (100 g.) was dissolved in 25% hydrochloric acid (500 c.c.), and 6-nitroquinoline (25 g.) added to the solution which was then heated on the water-bath for one hour. A white crystalline solid separated. After cooling, this solid was filtered off, dissolved in water and the solution made strongly alkaline with 10 $\bar{N}$ sodium hydroxide. A buff-coloured solid was precipitated, which was filtered, washed, dried and treated with charcoal in benzene solution. After recrystallising from a benzene-light petroleum (40-60°) mixture, 6-aminoquinoline was obtained as yellow needles, m.p. 116°. Yield - 15 g. (71% of theory).

4-(6^1-quinolylimino)-pentan-2-one.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

(a) A mixture of 6-aminoquinoline (1 g.), acetyl acetone (1 c.c.) and anhydrous calcium sulphate (1 g.) was heated on the water-bath for two hours. The mixture became viscid, and on extracting with alcohol, evaporating the solvent, and extracting the oily residue with ether, a pale yellow solid was obtained, m.p. 112-116°. This material was identical with the original 6-aminoquinoline.

(b) The experiment was repeated, a trace of iodine being added as catalyst, and the heating being continued for five hours. On cooling and scratching the resulting oil, a yellow solid was obtained. This was extracted with alcohol, yielding a brown solution with a green fluorescence. On adding water to this solution, a yellow solid crystallised as hexagonal plates, m.p. 102-5°. After several crystallisations from light petroleum (40-60°), 4-(6^1-quinolylimino)-pentan-2-one was obtained as yellow rods, m.p. 105-6°. Yield - 1.2 g. (76% of theory).

(Found: C - 74.05; H - 5.95; N - 12.65.

$C_{14}H_{14}ON_2$ requires C - 74.3; H - 6.2; N - 12.4.)

This compound gives a bright diazo reaction, probably due to hydrolysis by the hydrochloric acid.

Attempts to cyclize 4-(6^1-quinolylimino)-pentan-2-one.

(a) 4-(6^1-quinolylimino)-pentan-2-one (½ g.) was slowly added to concentrated sulphuric acid chilled to 2^o C, the acid being stirred during the addition. The solution, yellow in colour, was then heated on the water-bath for two minutes, and poured on to ice. A copious white precipitate formed immediately, but on standing, most of it dissolved, leaving a slight, buff residue. This was filtered off, and the filtrate made alkaline with 10 $\bar{N}$ sodium hydroxide. A whitish solid precipitated, which on crystallisation from benzene melted at 112-115^o (.2 g.). It gave a positive diazo reaction and did not depress the m.p. of an authentic specimen of 6-aminoquinoline. Hydrolysis of the anil to the free amine thus appeared to have taken place.

(b) 100% sulphuric acid was prepared by adding 20% oleum (8.9 g.) to 96% sulphuric acid (10 g.). The 100% acid was cooled to 2^o and 4-(6^1-quinolylimino)-pentan-2-one (½ g.) slowly added, with stirring. The yellow solution which was produced was heated on the water-bath for two minutes and then poured on to ice. A bright yellow solution was formed which, on making alkaline with 10 $\bar{N}$ sodium hydroxide, yielded a copious white precipitate. On diluting the

solution, this solid, probably sodium sulphate, dissolved, leaving a few mgs. of a dark grey solid which was filtered off. The filtrate, on re-acidification, again yielded a bright yellow colour, but no solid was precipitated. The solution was extracted in turn with ether, benzene and chloroform, but nothing dissolved in these solvents.

It was concluded that sulphonation had taken place, the sulphonated product being very soluble in water.

5-bromo-6-aminoquinoline.

(cf. Meigen, J. Prakt. Chem., 1906, 73, 248.)

6-aminoquinoline (14.4 g.) was dissolved in glacial acetic acid (75 c.c.), and a solution of bromine (3 c.c.) in 25 c.c. of the same solvent slowly added, the mixture being thoroughly stirred during the addition. The solution was allowed to stand over night. An orange solid separated which was filtered off, dissolved in water, and the solution basified with ammonia. A pale yellow solid was obtained which recrystallised from light petroleum (100-120°) as yellow needles, m.p. 126°.

The acetic acid mother liquors were also basified, yielding a yellow oily solid. On crystallising from the same solvent, a further small amount of 5-bromo-6-aminoquinoline was obtained. Yield - 11 g. (50% of theory).

Attempts to prepare 9-bromo-1:5-anthrazoline.

(cf. E.P. 394416.)

A mixture of 5-bromo-6-aminoquinoline (10 g.), 69% sulphuric acid (87.6 c.c.), glycerine (24 c.c.) and arsenic acid (20 c.c.) was refluxed for one hour, when a negative diazo reaction was obtained. The black solution was poured into water and made alkaline with 10 N-sodium hydroxide. A black oil floated to the surface. This was separated, and extracted with hot ether, a yellow solution being obtained. A considerable residue remained as a black tarry solid. The ethereal solution was dried and the solvent evaporated. A sticky, yellow solid was left which was extracted with hot light petroleum (60-80°). On cooling the extract, a very pale yellow solid separated, m.p. 159-166°. Yield - ½ g. After several crystallisations from the same solvent, white crystals were obtained, m.p. 175-7°, which did not depress the melting point of a pure specimen of p-phenanthroline.

On reducing the volume of the light petroleum extract still further, a small amount of a pale yellow solid separated, m.p. 125-130°. After crystallising this material several times from the same solvent, the melting point remained constant at 131-3° C. It

gave a + Beilstein reaction and a negative diazo test and was thought to be the desired 9-bromo-1:5-anthrazoline. However, it analysed as follows:

(Found: C - 64.0; H - 4.3; N - 12.3; Br - 21.45.

$C_{13}H_7N_2Br$ requires C - 55.6
H - 2.7
N - 10.8
Br - 30.9

Calculated for $C_{13}H_8N_2$ - C - 80.0
H - 4.44
N - 15.56.)

It was therefore concluded that this compound was a 35-65% mixture of p-phenanthroline and the desired bromo-anthrazoline.

The tarry residue insoluble in ether was extracted thoroughly with boiling benzene. Some of it dissolved, giving a yellow solution, but the bulk of the material remained as an insoluble, black, amorphous mass. On reducing the volume of the benzene, a yellow solid crystallised, m.p. 135-158°. This was fractionally crystallised from light petroleum (40-60°). Three fractions separated which gave the following products -

(1) White crystals, m.p. 170°, which on recrystallising from ether melted at 174-6°, and was identified as p-phenanthroline.

(2) Pale yellow crystals - a mixture of needles and plates, m.p. 165-172°.

(3) Pale yellow micro-crystals, m.p. 130-5°, which on recrystallisation from light petroleum (40-60°) melted at 132-3°, and did not depress the melting point of the analysed sample described above.

In an attempt to separate the p-phenanthroline and 9-bromo-1:5-anthrazoline, the mixture was dissolved in benzene and passed through an alumina column - 9" x ¾". A yellow band remained at the top of the column, colourless fractions being collected. On evaporating the benzene from the latter fractions, pure specimens of p-phenanthroline were obtained. Yield - 1 g.

The yellow band was eluted with benzene containing a small quantity of alcohol. A yellow solution was obtained from which, on reducing the volume, a pale yellow solid crystallised, m.p. 84-95°. Further crystallisations from benzene and light petroleum, however, raised the melting point again to 131-3°, the product being identical with that already described.

Lack of material prevented further purification.

(b) 5-bromo-6-aminoquinoline (5 g.), glycerol (5 c.c.), sodium m-nitrobenzene sulphonate (5 g.) and water (.6 c.c.) were mixed, and the mixture refluxed for two hours. After half-an-hour, the solution became black, and on pouring into water, a consider-

able quantity of black tar separated. This was filtered off, and the filtrate made alkaline with 10 N-sodium hydroxide. A brown solid precipitated which was filtered, dried and extracted with ether. On reducing the volume of the ether extract, a felt of yellow needles crystallised, m.p. 160-6°, which gave a positive Beilstein reaction and a negative diazo test. This was triturated with cold ether; the ether solution became yellow, leaving a white residue which on crystallising from light petroleum (40-60°) melted at 174-6°, and did not depress the melting point of an authentic specimen of p-phenanthroline. Yield - .4 g.

The yellow ethereal extract was treated with charcoal, and the volume reduced. A small quantity of white filamentous needles was obtained, which after several crystallisations from light petroleum (40-60°) softened at 136° and melted at 140-1°. On cooling the melt and reheating, the melting point was found to be 138-9°. This material gave the following analytical results:

Found: C - 62.77; H - 2.99, which corresponds to a mixture of 75% of 9-bromo-1:5-anthrazoline and 25% p-phenanthroline. This would explain the sharpening of the melting point, as p-phenanthroline sublimes on heating. However, attempts to purify the

mixture by sublimation were unsuccessful, prolonged heating on an oil-bath at 140° under reduced pressure resulting in extensive decomposition.

Attempts to prepare 4-(5^1-bromo-6^1-quinolylimino)-pentan-2-one.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

A mixture of 5-bromo-6-aminoquinoline, anhydrous calcium sulphate, acetyl acetone and a trace of iodine was heated on the water-bath for six hours. The mixture became dark brown, and did not solidify on cooling and scratching. On extraction with alcohol, a brown solution with a green fluorescence was obtained, which yielded a brown oil. On distilling off the alcohol most of the oil dissolved on extraction with hot light petroleum (40-60°). On cooling the solution, yellow needles crystallised, m.p. 124-6°, which did not depress the m.p. of the original 5-bromo-6-aminoquinoline. No condensation therefore appeared to have been effected.

The experiment was repeated, the mixture being heated at 130° for six hours, and on the water-bath for two days, but in both cases, the original amine was recovered.

5-chloro-6-aminoquinoline.

(cf. Kern - Dissertation, Freiburg, 1906, 87.)

Three different types of experiment were carried out:-

(a) 6-aminoquinoline (2 g.) was dissolved in glacial acetic acid (25 c.c.), and chlorine, prepared by the action of cold, concentrated hydrochloric acid on potassium permanganate, washed and dried, was bubbled slowly through the solution until the desired increase in weight (1 g.) was observed. The solution became quite hot, and a small amount of crystalline material was formed which was filtered, washed with glacial acetic acid, suspended in water, and treated with ammonia. A greyish solid (.2 g.) was obtained which melted at approximately 220°. This material gave a positive Beilstein reaction but a negative diazo test.

The acid mother-liquors, on pouring into water, formed a yellow precipitate, which was filtered off, suspended in water and basified with ammonia. A pale, greenish-yellow solid was obtained, insoluble in benzene, light petroleum and acetone, and only slightly soluble in alcohol. Recrystallisation from alcohol yielded greyish-white needles (.3 g.) which darkened at 230° and melted at 235°. Again, however, this material gave a positive Beilstein

reaction but a negative diazo test, and so was not the desired 5-chloro-6-aminoquinoline.

(b) Chlorine, prepared as in the last experiment, was bubbled into glacial acetic acid (25 c.c.) until an increase in weight of 1 g. was observed. This solution was slowly added to a stirred, cooled solution of 6-aminoquinoline (2 g.) in glacial acetic acid, and the mixture allowed to stand for one hour. The solution became an inky-black colour and no precipitate was formed. On pouring this into water, a dark-brown solution was obtained, which, on making alkaline, yielded an oily, red-brown precipitate. This was filtered off, extracted with alcohol, the solvent evaporated, and the dark-brown oil which remained was extracted with hot light petroleum (40-60°). On cooling, a small amount of yellow solid crystallised from this solution, m.p. 115-118°, which after two crystallisations from benzene melted at 120-6°. This material gave both a positive Beilstein reaction and a positive diazo test, and so was probably 5-chloro-6-aminoquinoline, but the small amount obtained prevented further purification.

(c) 6-acetylaminoquinoline was prepared by heating a mixture of 6-aminoquinoline (5 g.) and acetic anhydride (4 c.c.) on the water-bath, a drop of

concentrated sulphuric acid being added as catalyst. After one hour, the mixture was poured into water, giving a brown solution, which on neutralising with sodium carbonate yielded a light-brown precipitate which crystallised from aqueous alcohol as yellow needles, m.p. 74°. Yield - 6.3 g. (98% of theory).

Chlorine (2 g.) was dissolved in glacial acetic acid (25 c.c.), and the mixture slowly added to a well-stirred solution of 6-acetylaminoquinoline (5.2 g.) in the same solvent. A buff-coloured precipitate began to form almost immediately. The pasty mixture was allowed to stand for an hour, then poured into water, when it dissolved to give a pale yellow solution. On neutralising with sodium carbonate, a white solid was precipitated, a specimen of which crystallised from aqueous alcohol as rods, m.p. 162°.

The crude white solid was now dissolved in a small quantity of alcohol, an equal volume of concentrated hydrochloric acid was added, and the mixture heated on the water-bath for an hour. The solution was then poured into water and basified with ammonia. A silvery white solid precipitated which crystallised from aqueous alcohol in rhombs, m.p. 115-124°. Recrystallisation from water gave greyish-white needles, 125-7° m.p. (Kern quotes m.p. 128°.) Yield - 3 g. (60% of theory).

This compound gave a positive Beilstein reaction and a positive diazo test, and as the m.p. was in close proximity to that quoted by Kern, it was concluded to be 5-chloro-6-aminoquinoline.

It is soluble in ether, benzene, alcohol and light petroleum.

9-chloro-1:5-anthrazoline.

(cf. E.P. 394416.)

5-chloro-6-acetylaminoquinoline (10 g.) was mixed with 69% sulphuric acid (87.6 c.c.), glycerine (24 c.c.) and arsenic acid (20 c.c.), and the mixture heated under reflux. After half-an-hour a positive diazo test was obtained. Diazo tests were carried out half-hourly, and only after six hours did the test become negative. The inky-black solution was poured into water and made alkaline with 10 $\bar{N}$ sodium hydroxide. A black oil formed which, on cooling, solidified to a hard, black crust. This was extracted with alcohol, the solvent evaporated, and the resulting tar extracted with acetone. A reddish-purple solution was obtained, which was treated with dry hydrogen chloride. A reddish-brown hydrochloride formed which on filtering proved to be hygroscopic. It was therefore dissolved in water and the solution basified with 2 $\bar{N}$ sodium hydroxide. The oil which formed was extracted with light petroleum (40-60°), the solution dried and then reduced in volume. A very small quantity of yellow needles crystallised, which after several crystallisations from the same solvent melted at 162-3°. This compound gave a positive Beilstein reaction and a negative diazo test,

and analysed as follows:-

(Found: C - 64.35; H - 3.65.

$C_{17}H_7N_2Cl$, $\frac{1}{2}$ H_2O requires C - 64.4
H - 3.6.)

This compound therefore appeared to be 9-chloro-1:5-anthrazoline, but the yield was so small as to be impracticable for further use.

(b) 5-chloro-6-aminoquinoline (3 g.) was mixed with 69% sulphuric acid (25 c.c.), glycerol (3 c.c.) and sodium m-nitrobenzene sulphonate (3 g.), and the mixture heated under reflux. The solution became very black, and after fifty minutes, a negative diazo reaction was obtained. The solution was then poured into water and made alkaline with 10 $\bar{N}$-sodium hydroxide. A black oil separated which was extracted with alcohol. On distilling off the alcohol, a dark brown oil was obtained, which on extraction with ether yielded a pink solution from which a pink solid crystallised ($\frac{1}{2}$ g.). On crystallising this material from light petroleum (40-60°) white needles were obtained, m.p. 174-6°, identified as p-phenanthroline. The reddish oily residue, insoluble in ether, was dissolved in benzene, and solutions of oxalic acid, picric acid, and phthalic acid added in turn, but in every case, oily products were obtained.

(c) A mixture of 5-chloro-6-acetylaminoquinoline (5 g.), concentrated sulphuric acid (5 c.c.), glycerine (12 c.c.), arsenic acid (10 c.c.) and ferrous sulphate (1 g.) was warmed until it began to froth. The bunsen was removed until the vigorous reaction had ceased, and then the mixture was refluxed for six hours. No tarring took place. Although the diazo test was still positive, the mixture was poured into water and worked up as before. The only product isolated was 5-chloro-6-aminoquinoline (2 g.). Only hydrolysis to the amine appeared to have taken place.

Attempts to prepare 4-(5^{1}-chloro-6^{1}-quinolylimino)-pentan-2-one.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

A mixture of 5-chloro-6-aminoquinoline (1 g.), acetyl acetone (1 c.c.), anhydrous calcium sulphate and a trace of iodine were heated on the water-bath for six hours. The oily mixture was then extracted with alcohol, and the solvent distilled off from the resulting solution. A brown oil was obtained, which on extraction with hot light petroleum (40-60°) and reducing the volume of the extract, yielded pale yellow needles, m.p. 124-6°, identical with the original 5-chloro-6-aminoquinoline.

No condensation appeared to have taken place.

Ethyl-β-(5^1-chloro-6^1-quinolylamino)-α-carbethoxy acrylate.

A mixture of ethoxy methylene malonate (3 c.c.) and 5-chloro-6-aminoquinoline (2.3 g.) was heated on the water-bath under reduced pressure. The solution bubbled vigorously, and after half-an-hour, a yellow solid was formed. This was extracted with alcohol, giving a yellow solution with a green fluorescence. On reducing the volume of this solution, a pale yellow solid crystallised, melting at approximately 150°. Further crystallisations from alcohol yielded ethyl-β-(5^1-chloro-6^1-quinolylamino)-α-carbethoxy-acrylate as pale yellow needles, m.p. 153-154°. Yield - $2\frac{1}{2}$ g.

(Found: C - 58.5; H - 5.2; N - 7.95; Cl - 10.7.

$C_{17}H_{17}N_2ClO_4$ requires C - 58.5
H - 4.9
N - 8.0
Cl - 10.2.)

Attempts to prepare 4-hydroxy-3-carbethoxy-9-chloro-1:5 anthrazoline.

(a) Ethyl-β-(5¹-chloro-6¹-quinolylamino)-α-carbethoxy acrylate (1 g.) was dropped into boiling diphenyl (10 g.) and the mixture refluxed for half-an-hour using a very short air-condenser to allow any alcohol formed to escape. The solution became brown and then very black. It was allowed to cool and then treated with light petroleum (40-60°), which dissolved the diphenyl, leaving a dark-brown amorphous residue. This was extracted with hot alcohol, a considerable black insoluble tar being left. The alcohol solution was treated with charcoal and reduced in volume, when a very small quantity (mgs.) of a greenish-yellow solid crystallized, m.p. 260-71°. On further crystallisations, this material melted at 261-3°, but the amount was too small for further examination.

The alcohol mother liquors were diluted with water. A light-brown oily solid separated, which was filtered off and recrystallised from alcohol as pale yellow needles, m.p. 153°, identical with the original acrylate.

(b) The experiment was repeated, the mixture being boiled in diphenyl for one hour. It again became

very black, and on treatment with light petroleum the diphenyl dissolved leaving a dark-brown residue. This was filtered off, extracted with hot alcohol, the extract treated with charcoal and the solvent distilled off. A bright yellow solid was left, but on triturating with cold alcohol, the yellow colour was removed and a white solid remained. This material was soluble in water, sublimed above 300° and gave off ammonia when heated with sodium hydroxide. It was therefore concluded that this solid was ammonium chloride which must have resulted from extensive decomposition of the acrylate.

On removing the solvent from the cold alcohol extract, a small amount of yellow oil was obtained which failed to crystallise from a variety of solvents.

(c) Cyclization was also attempted by placing a hard-glass test-tube containing ethyl-β-(5¹-chloro-6¹-quinolylamino)-α-carbethoxy acrylate into a metal bath at 300° for two minutes. Yellow fumes poured from the mouth of the tube. A black oil remained which was extracted with hot ligroin (100-120°). Pale yellow needles crystallised on cooling, m.p. 153°, identical with the original acrylate.

4-(5^1-methyl-8^1-hydroxy-6^1-quinolylimino)-pentan-2-one.

(cf. Johnson and Mathews, J.A.C.S., 1944, 66, 210.)

A mixture of 5-methyl-7-amino-8-hydroxy quinoline (½ g.), acetyl acetone (1 c.c.) and anhydrous calcium sulphate (1 g.), with a trace of iodine as catalyst, was heated on the water-bath, solidification taking place within a few minutes. The pinkish mixture was extracted with alcohol and the volume reduced. The pinkish solid which separated crystallised from alcohol as rods m.p. 184-5°, which gave a brown-green colour with ferric chloride.

Found: C - 69.50; H - 5.9; N - 10.5.

$C_{15}H_{16}N_2O_2$ requires C - 70.3
H - 6.25
H - 10.9

The analyst reported a slight white ash which would account for the low analysis and which might have been due to a trace of calcium sulphate which had come through the filter paper.

Attempts to prepare 2:4-dimethyl-9-diethylaminoethylamino-1-azanthracene.

(a) A mixture of phenol (10 g.) and diethylaminoethylamine (1 g.) was dried on the water-bath under reduced pressure for three hours, 9-bromo-2:4-dimethyl-1-azanthracene (1 g.) added, and heating continued for a further three hours. On testing a portion of the mixture with silver nitrate in the presence of nitric acid, a copious white precipitate was obtained.

The mixture was poured in to 2 N sodium hydroxide, and the oily yellowish precipitate extracted thoroughly with ether, the solution being red-brown in colour, while the sodium hydroxide retained a dark blue fluorescence. The ethereal solution was extracted with 2 N. acetic acid, a yellow solution with a green fluorescence being obtained. On basifying with ammonia, the solution became opalescent and was extracted with ether. The ether extract was dried over anhydrous potassium carbonate and the solvent distilled off. A red-brown oil which remained resisted all attempts at crystallisation, so it was redissolved in ether and an ethereal solution of oxalic acid added. A yellow solid separated, which after crystallising several times from alcohol was obtained as

yellow needles, darkening at 169° and melting at 175°. The yield was of the order of mg. This compound analysed as follows -

Found: C - 62.65; H - 5.4; N - 5.4.

A similar experiment was carried out in which the mixture was heated at 190° for fifteen hours. The product was worked up in the same manner and yielded an identical oxalate in better yield - .3 g.

(b) A mixture of 9-bromo-2:4-dimethyl-1-azanthracene (2 g.), diethylaminoethylamine (2 g.), alcohol (15 c.c.), with traces of copper bronze and potassium iodide as catalysts, was heated in a sealed tube at 180-210° for twenty-four hours. A white sublimate formed at the sealed end of the tube. On opening the tube, a strong odour of ammonia was detected. The white sublimate proved to be deliquescent, and effervesced with dilute acid. It gave a negative halogen test, and so was most probably ammonium carbonate.

The alcoholic solution in the tube was filtered, and the solvent distilled off. The black tarry residue was thoroughly extracted with ether, a brown solution with a green fluorescence being obtained. On distilling off the ether, a reddish oil remained which resisted attempts to crystallise it. The oil

was therefore dissolved in ether, and treated with an ethereal solution of oxalic acid. A yellow oxalate formed which was filtered and, after several crystallisations from alcohol, was obtained as balls of needles which darkened at 180° and melted at 181-2°. This product gave a negative Beilstein reaction and did not depress the melting point of the oxalate obtained in the last experiment.

This oxalate, which exhibited a green fluorescence in alcohol, analysed as follows -

Found: C - 62.9; H - 5.4; N - 5.75.
(cf. analytical results in (a))

$C_{32}H_{29}N_3$ requires C - 62.9
H - 4.8
N - 5.8.

These results, discussed earlier in this thesis, suggest that this compound may be the trioxalate of bis-(2:4-dimethyl-1-azanthracyl)-ethylamine.

Attempts to prepare 9-amino-2:4-dimethyl-1-azanthracene.

(cf. Haworth and Sykes, J.C.S., 1944, 311.)

(a) 9-bromo-2:4-dimethyl-1-azanthracene (3 g.) was mixed with phenol (3 g.), concentrated ammonia (10 c.c.) and copper sulphate (.3 g.) and the mixture heated in a sealed tube at 300° for three days. On cooling, a black, tarry semi-solid material separated. The supernatant liquid was decanted and the residue washed and extracted several times with dilute hydrochloric acid. There was a large, insoluble residue at this point. On basifying the acid solution, a yellow, oily suspension was formed, from which a brown oil deposited on standing. This oil was separated and extracted with alcohol, yielding a brown solution with a deep blue fluorescence. On treating this solution with an alcoholic solution of hydrogen chloride, a dark red hydrochloride separated which was very soluble in water, giving a blood-red solution, and which crystallised from dilute hydrochloric acid as blunt rods m.p. 285°. The small yield of this hydrochloride prevented further purification.

(b) A mixture of 9-bromo-2:4-dimethyl-1-azanthracene (3 g.), concentrated ammonia (8 c.c.) and copper

bronze (.3 g.) was heated in a sealed tube at 200-230° for twelve hours. On cooling, a black, brittle mass separated, which was filtered, washed free from ammonia, and extracted with alcohol, giving a brown solution with a blue fluorescence. A black insoluble residue (1 g.) was left. On adding an alcohol solution of hydrogen chloride to this solution, a dark-red hydrochloride separated which crystallised from a very small volume of water as rods m.p. 285°, identical with the hydrochloride obtained in small yield in the last experiment. This hydrochloride dissolved in water, giving a blood-red solution which, on adding more acid, turned yellow. Careful addition of dilute ammonia restored the red colour, so it was concluded that colour change from red to yellow indicated the formation of a higher hydrochloride.

On making the aqueous solution of the hydrochloride alkaline with ammonia, the red colour was discharged, and an orange solid precipitated. This solid crystallised from light petroleum as rhombs m.p. 125-6° and gave both a negative Beilstein test and a negative diazo reaction. It analysed as follows -

Found: C - 83.9; H - 5.9; N - 9.7

$C_{30}H_{25}N_3$ requires C - 84.3
H - 5.85
N - 9.8.

The formulation of this compound as bis-(2:4-dimethyl-1-azanthracyl)-amine has been discussed earlier in this thesis.

(c) A mixture of 9-bromo-2:4-dimethyl-1-azanthracene (5 g.), concentrated ammonia (13 c.c.) and copper bronze (.3 g.) was heated in a sealed tube at 140° for twenty-four hours. On cooling, a mixture of a semi-solid black material and white crystals separated at the foot of the tube. This was filtered, and on washing with water, the white crystals dissolved. The black residue was extracted with alcohol, giving a brown solution with a blue fluorescence and leaving a considerable insoluble residue. Addition of an alcoholic solution of hydrogen chloride precipitated a small amount of a dark red solid, identical with that obtained in the experiments carried out at the higher temperature as already described. This was filtered off, and the alcohol evaporated from the mother liquors. The dark oil which remained was dissolved in ether, and dry hydrogen chloride passed into the solution. A bright yellow solid was formed, which, on filtering, became orange, and on standing formed a dark-brown oil. The oil was therefore dissolved in water and the solution made alkaline with ammonia. A brown oil was precipitated which, on standing overnight in the refri-

gerator, formed a semi-solid mass. This was extracted with light petroleum (40-60°), yielding a yellow solution from which yellow diamond-shaped crystals deposited, m.p. 135-170°. Yield 2.4 g. Crystallisation from various solvents did not sharpen the melting point.

The solid was therefore dissolved in benzene and passed into an alumina column (9" x ¾") in the same solvent. At first, four indistinct bands appeared - yellow, orange, purplish and green in colour. The yellow band was washed through with benzene and on distilled off the benzene from the fractions collected, pale yellow crystals m.p. 166-168° were obtained (1.9 g.), which did not depress the melting point of a specimen of the original 9-bromo-2:4-dimethyl-1-azanthracene.

The column was then washed with benzene containing increasing amounts of alcohol, and finally with pure alcohol. The various fractions collected, on reducing the volume, yielded specimens of yellow solids, melting in the range of 159-176°. On removing the alcohol from the mother liquors obtained on filtering off this solid, a deep orange, oily solid was left. Both these products were again chromatographed, using an alumina column and benzene as solvent.

The yellow solid, m.p. 159-176°, appeared to separate into two bands at the top of the column, but on passing further down they merged and were collected as an orange solution from which an orange solid, melting from 186-90°, crystallised on reducing the volume. Crystallisation from alcohol did not sharpen the melting point. However, this compound gave a negative Beilstein test, and with alkaline sodium hydrosulphite, a purple vat was obtained, suggesting the presence of a quinone structure. This compound may thus have been an impure specimen of 2:4-dimethyl-1-azanthraquinone (m.p. 205-16°).

The orange oil separated into three distinct bands. A yellow band passed quickly down the column yielding a yellow solution with a purple fluorescence, from which, on reducing the volume, a pale yellow solid crystallised, m.p. 164-7°. This compound did not depress the melting point of a specimen of the original 9-bromo-2:4-dimethyl-1-azanthracene. Yield .1 g.

An orange band moved more slowly through the column and was collected as an orange solution. On removing the benzene, an orange oil remained which solidified to a pinkish-orange solid after scratching. Extraction with hot light petroleum (40-60°) gave a yellow solution from which buff coloured

needles separated on cooling. A pink oily residue was left which resisted all attempts to crystallise it. The buff needles on further crystallisation from light petroleum (40-60°) melted at 85-6°, and did not depress the melting point of a specimen of 2:4-dimethyl-1-azanthracene, prepared by a Combes' synthesis on β-naphthylamine.

Summary of products isolated -

(1) Unchanged 9-bromo-2:4-dimethyl-1-azanthracene.

(2) Bis-(2:4-dimethyl-1-azanthracyl)-amine.

(3) Aquinone, probably 2:4-dimethyl-1-azanthraquinone.

(4) 2:4-dimethyl-1-azanthracene.

(d) An experiment was carried out, alcohol being added to the mixture of 9-bromo-2:4-dimethyl-1-azanthracene, ammonia and copper bronze, which was then heated in a sealed tube at 200° for twelve hours. The only product isolated was some bis-(2:4-dimethyl-1-azanthracyl)-amine.

(e) A mixture of 9-bromo-2:4-dimethyl-1-azanthracene (1 g.), phenol (10 g.), and a trace of copper bronze was heated in an oil-bath at 180°, and ammonia was slowly bubbled through the solution for four hours. The mixture became dark green and finally black. A small quantity of white crystals separated

on the sides of the flask, which may have been ammonium bromide. On cooling, the black mixture was treated with 2 N. sodium hydroxide. The phenol dissolved, leaving a black oil which was extracted with ether, yielding a reddish-brown solution and leaving a black tarry residue representing the bulk of the material. On removing the ether from the solution, a reddish oil remained. This was extracted with light petroleum (60-80°), and the volume of the solution reduced. A red oil was precipitated first, and on further reducing the volume, a yellow solid was obtained, melting at approximately 160°, which proved to be some of the original 9-bromo-2:4-dimethyl-1-azanthracene (.1 g.). A further quantity of this material was obtained on re-extracting the red oil with light petroleum (60-80°) and again reducing the volume. This process was repeated until only a very small amount of red oil was left. On dissolving the oil in ether, and adding ethereal solutions of oxalic acid and picric acid, oily products were obtained. This oil gave a negative diazo reaction.

Attempts to prepare 1-iodo-β-naphthylamine.

(cf. Willstaedt and Schreiber, Ber., 1934, 67, 466.)

(a) N-acetyl-β-naphthylamine (5 g.) was dissolved in glacial acetic acid (20 c.c.), and a solution of iodine monochloride in the same solvent was slowly added with stirring. A brown paste crystallised out before the addition was complete. The mixture was allowed to stand for half-an-hour and then poured into a large volume of water. The brownish precipitate was filtered, washed, and after several crystallisations from alcohol yielded 1-iodo-N-acetyl-β-naphthylamine as white needles m.p. 164°. (Willstaedt and Schreiber quote m.p. 167°, darkening at 140°.)

1-iodo-N-acetyl-β-naphthylamine was dissolved in alcohol, concentrated hydrochloric acid (100 c.c.) slowly added with stirring, and the mixture refluxed for three hours. Violet vapours appeared above the liquid and escaped through the condenser; they turned starch solution blue and smelled strongly of free iodine. The mixture was allowed to stand over night and in the morning the flask was found to be filled with a black crystalline mass. This was filtered off and extracted with boiling ammonium hydroxide. The thick black oil which was formed in considerable amount was separated, and the ammoniacal liquors cool-

ed. Shining white plates deposited, m.p. 108°, which on crystallising from alcohol melted at 110-112°. This product gave a positive diazo reaction but a negative Beilstein test, and did not depress the melting point of an authentic specimen of β-naphthylamine (112°).

The black oil, which was insoluble in ammonia, dissolved in alcohol, giving a black solution which had a strong odour of iodine.

These results have been discussed earlier in the theoretical section of this thesis.

(b) The experiment was repeated, but the hydrolysis of 1-iodo-N-acetyl-β-naphthylamine was attempted with sulphuric acid of varying strengths - 75%, 50% and 25%. In every case, iodine was liberated, and β-naphthylamine crystallised from the ammoniacal liquors, just as in the previous experiment.

(c) 1-iodo-N-acetyl-β-naphthylamine (5 g.), prepared as in (a), was refluxed with alcohol potassium hydroxide (25 c.c.) for three hours. On pouring into water, an oily solid separated which solidified on standing. This was filtered and extracted with water. White needles, m.p. 128-130°, crystallised from the aqueous solution which gave a negative Beilstein test and a negative diazo reaction, and which did not depress the melting point of an

authentic specimen of N-acetyl-β-naphthylamine. The residue, insoluble in water, was extracted with benzene. On evaporating off the solvent, a small amount of oil was obtained which gave a positive Beilstein reaction and a positive diazo test. However, all attempts to isolate a crystalline product from this material by extraction with ether and light petroleum were unsuccessful.

(d) N-acetyl-β-naphthylamine (5 g.) was dissolved in glacial acetic acid (50 c.c.) and a solution of iodine (6.9 g.) in the same solvent was slowly added with stirring. After standing for half-an-hour the mixture was poured into water, when a violet solid was precipitated. This was filtered, dissolved in alcohol and an equal volume of concentrated hydrochloric acid added. A pinkish crystalline mass separated, which was filtered, dissolved in water and made alkaline with ammonia. The whitish solid which precipitated crystallised from water as white glistening plates, m.p. 112°. This material did not depress the melting point of an authentic specimen of β-naphthylamine.

(e) (i) Benzal-β-naphthylamine.

β-naphthylamine (5.4 g.) was dissolved in ethyl alcohol (15 c.c.) and benzaldehyde (4.25 g.)

added with stirring over a period of ten minutes, the temperature of the mixture being maintained at 70°. The mixture was kept at this temperature for a further five minutes and then allowed to cool. The yellow solid was then filtered, washed with alcohol and crystallised from alcohol, yielding pale yellow crystals m.p. 101-3°. Yield - 7.2 g.

(ii) Benzal-β-naphthylamine (5 g.) was dissolved in chloroform (15 c.c.), and a solution of iodine monochloride (1 c.c.) in chloroform (5 c.c.) dropped in, the mixture being thoroughly stirred during the addition. While the first half of the iodine monochloride solution was being added, the temperature remained at 18°, but on further addition, it began to rise, so the flask was cooled in water to keep the temperature of the mixture below 25°. At first, a yellow solid precipitated, but this later changed to an olive-green mixture of oil and solid. On adding light petroleum to the mixture, the oil solidified and the resulting solid was filtered off. On warming with water or dilute alkali, however, a dark-brown oil was obtained, which was dissolved in alcohol and treated with alcoholic hydrogen chloride. A bright yellow solid separated, but on standing, this product turned dark green and eventually brown. It was therefore reconverted to the base by treatment with alkali, and a portion of the oil so obtain-

ed was boiled with benzoyl chloride and 10% sodium hydroxide. A dark brown solid was formed, which after several crystallisations from alcohol gave greyish-white rods, softening at 145° and melting at 153°. This product gave a positive Beilstein test, but a quantitative analysis showed that the iodine content was less than 1%.

A portion of the oil was also allowed to stand in the cold over night with acetic anhydride. On pouring the resulting mixture into water, a brown solid separated. This was extracted with alcohol, the solution treated with charcoal and reduced in volume. A small quantity of white crystals deposited which after crystallising several times from alcohol melted at 164°, and did not depress the melting point of 1-iodo-N-acetyl-β-naphthylamine, prepared previously.

The remainder of the oil was extracted with light petroleum and, on removing the solvent, the orange-oil which remained was allowed to stand in the refrigerator for a time. A semi-solid brown mass formed which on crystallising from alcohol gave pale yellow needles m.p. 97-8° which did not depress the melting point of an authentic specimen of benzal-β-naphthylamine.

These results have been discussed earlier in the theoretical section.

(f) (i) β-naphthyl-phthalimide.

Phthalic anhydride (5 g.) and β-naphthylamine (5 g.) were added to nitrobenzene (50 c.c.), the mixture refluxed for two hours and then allowed to stand over night. A yellow crystalline mass separated, which gave a negative diazo reaction, and crystallised from benzene as white rods m.p. 219°, yield 8 g.

(ii) β-naphthyl-phthalimide (5 g.) was dissolved in chloroform (25 c.c.), and a solution of iodine monochloride (1 c.c.) in chloroform (10 c.c.) added with stirring. No obvious change took place, and on standing over night, no precipitate separated. The mixture was therefore refluxed for two hours and then cooled, but again no precipitate was obtained. The chloroform was distilled off and the oily residue crystallised from alcohol, when white needles were obtained m.p. 219°, identical with the original β-naphthyl phthalimide (4.4 g.).

(g) β-naphthylamine (10 g.) was dissolved in 50% acetic acid, and a solution of iodine monochloride (3.5 c.c.) in the same solvent slowly added. A brownish-green precipitate separated, which was filtered off, and on treatment with alkali gave a mixture of a white solid and a black oil. The solid crystallised from water as white plates, m.p. 110°,

and proved to be some of the original β-naphthylamine (2 g.).

The black oil yielded no crystalline product after various attempted crystallisations for benzene, ether, alcohol and light petroleum.

Tests carried out on 1-iodo-N-acetyl-β-naphthyl-amine for the liberation of iodine in the presence of acid.

A 5% solution of N-acetyl-β-naphthylamine was prepared. Then to one part of this solution was added nine parts of N/10, N, and 2 N hydrochloric acid respectively. A trace of starch was also added, then one set of these tubes was kept at room temperature and one set placed in an incubator at 37°.

Overnight, the incubated tubes containing N and 2 N acid produced a blue colour; six hours later, the tube containing N/10 acid turned blue. No change was observed in the tubes kept at room temperature over the same period, but after three days, the tubes containing N and 2 N acid turned blue, and at the end of a week, the N/10 tube also produced a blue colour.

The conclusions drawn from these experiments have been discussed previously.

3-chloro-2-naphthoic acid.

(cf. Hosaeus, Ber., 26, 668.
cf. Strohbach, Ber., 34, 416.
cf. U.S. 2, 394, 279, Feb. 5, 1946.)

3-hydroxy-2-naphthoic acid (30 g.) was slowly added to a mixture of phosphorus pentachloride (100 g.), phosphorus oxychloride (50 c.c.), and a trace of "cetablon". Copious fumes of hydrochloric acid were evolved as the acid chloride was formed. The mixture was then refluxed in an oil-bath at 160-170° for six hours, the phosphorus oxychloride distilled off, and the resulting dark brown, oily residue poured into water. The mixture of oil and water was warmed slightly to hydrolyse the acid chloride of the resulting chloro acid, the latter itself then being obtained as a pale yellow solid. This was filtered off, purified by extraction with ammonia and reprecipitation with hydrochloric acid, and recrystallised from aqueous alcohol as very pale yellow needles. M.p. - 216°. Yield - 26½ gms. (73% of theory).

Two experiments were also carried out using the methods recommended by Hosaeus,(Ber. 26, 668), and Strohbach,(Ber., 34, 416). In both cases 3-hydroxy-2-naphthoic acid (30 g.) and phosphorus pentachloride (100 g.) were mixed and heated in an oil bath at 200-210° , the phosphorus oxychloride produced in the

course of the reaction being allowed to distil over.

In one experiment, the residue was poured into water, giving a black tar, which, on warming slightly, yielded a dark brown solid. This was very difficult to purify; extraction with alkali, treatment with charcoal and reprecipitation with acid gave a dark brown muddy solid, which filtered very slowly. As 3-chloro-2-naphthoic acid is very soluble in ether, it was found best to extract the brown solid in the cold with ether, a large residue being insoluble. On evaporating off the ether, 5 g. of 3-chloro-2-naphthoic acid was obtained.

Using Strohbach's method, the residue, after removing the phosphorus oxychloride by distillation, was distilled under as low a vacuum as possible. Some acid chloride did distil over and on hydrolysis gave a very pure specimen of 3-chloro-2-naphthoic acid, m.p. 216°, but so much tarring took place that this method was unsuitable for preparative work.

3-(m-chloro-anilino)-2-naphthoic acid.

(cf. Ullmann, Ann., 1907, 355, 340.
cf. Bachmann, J. Org. Chem., 1948, 13, 89.)

3-chloro-2-naphthoic acid (2 g.), m-chloro-aniline (4.25 g.), anhydrous potassium carbonate (1.59), copper bronze (.129), amyl alcohol (40 c.c.) and a trace of potassium iodide were mixed and refluxed for six hours in an oil bath at 150°. The mixture became dark green and finally brown. On cooling, a greenish-yellow solid separated. This was filtered off, washed thoroughly with acetone, and the residue, now buff-coloured, extracted with 2 N-sodium carbonate. The alkaline solution was then acidified with hydrochloric acid, when a small amount of yellow solid, melting at approximately 180°, was precipitated. On recrystallising this material from aqueous alcohol several times the melting point rose to 220°, and a negative Beilstein test was obtained. With neutral ferric chloride a deep blue colour was produced. These properties indicated that the solid was 3-hydroxy-2-naphthoic acid. A mixed melting point with an authentic specimen of the hydroxy-acid confirmed its identity.

The amyl alcohol and acetone washings were steam distilled, leaving behind a black oil. This oil was

extracted with dilute sodium carbonate and the hot extract acidified with acetic acid. The canary yellow solid which separated was filtered off and the filtrate made acid with hydrochloric acid. A pale yellow solid separated in small yield. This solid was filtered and recrystallised from aqueous alcohol as yellow needles, m.p. 216°, identical with the original 3-chloro-2-naphthoic acid.

The canary yellow solid precipitated by the acetic acid was recrystallised from aqueous alcohol, benzene and finally alcohol, when the melting point remained constant at 227-229° C. Yield - 5½ gms. - 72% of theory. Analysis confirmed the identity of this compound as 3-(m-chloroanilino)-2-naphthoic acid.

(Found: C - 67.5; H - 4.3; N - 4.4;

$C_{17}H_{12}O_2N\,Cl$, $\frac{1}{2}\,C_2H_6O$ requires C - 67.4
H - 4.7
N - 4.4.)

3-(m-chloro-anilino)-2-naphthoic acid is soluble in alcohol, dilute alkalis, ether, benzene and glacial acetic acid. It also dissolves easily in cold concentrated sulphuric acid from which it is precipitated by the addition of water. It is insoluble in dilute acids.

The cyclization of 3-(m-chloro-anilino)-2-naphthoic acid 5:6-dichloro 2:3-benzacridine and 5:8-dichloro 2:3-benzacridine.

3-(m-chloro-anilino)-2-naphthoic acid (4 g.) was added to phosphorus oxychloride (40 c.c.), and the mixture heated in an oil bath at 150° for two hours. The solution became dark purple in colour and on distilling off the phosphorus oxychloride, a dark purple, oily residue was left. This was cooled and slowly poured into a mixture of chloroform, ice and concentrated ammonia. The chloroform layer was coloured orange and a green fluorescence was observed. This layer was separated, washed with water, dried over anhydrous sodium sulphate and the chloroform distilled off. A reddish-orange solid remained. Yield - 3½ g. This was fractionally crystallised from dry benzene.

Four fractions were obtained -

1. light orange needles - m.p. 210-220°
2. deep orange crystals - m.p. 180-200°
3. orange-red crystals - m.p. 150-165°
4. a dark brown amorphous mass.

The first fraction, after several crystallisations from light petroleum (60-80°), was obtained as clusters of long, pale-orange needles, melting with decomposition at 231-2°. The following analytical

results were obtained for this compound -

Found: C - 68.5; H - 3.2; N - 4.8.

$C_{17}H_9NCl_2$ requires C - 68.4
H - 3.0
N - 4.7.

It therefore appeared to be a dichloro-benzacridine.

The solids from the second and third fractions did not melt sharply after several crystallisations, so it was decided to chromatograph the mixture. Dissolving the isomers in benzene and passing them into an alumina column suspended in benzene effected no separation, the material passing right through without being absorbed.

Another alumina column was therefore prepared, a fifty per cent mixture of benzene and light petroleum ($60-80^{\circ}$) being used as solvent. This time a separation was obtained, a light orange band passing quickly through, giving an orange solution with a green fluorescence, from which, on distilling off the solvent, a further specimen of the orange crystals m.p. $231-2^{\circ}$ was obtained. A reddish-orange band was strongly adsorbed at the top of the column and moved only very slowly. After the light orange band had been completely washed through, the column was therefore extruded and the reddish-orange band extracted with benzene. The solvent was evaporated and the residue after several crystallisations from light

petroleum (60-80°) yielded reddish-orange needles m.p. 180±5° which analysed as follows -

Found: C - 68.4; H - 3.2; N - 4.8.

$C_{17}H_9NCl_2$ requires C - 68.4
H - 3.0
N - 4.7.

The isomers were obtained in approximately equal quantities.

Properties:

(a) The light orange isomer m.p. 231-2° was sparingly soluble in alcohol, giving an orange solution with slight green fluorescence. It dissolved easily in ether and benzene, giving a yellow solution with a brilliant yellowish-green fluorescence. On warming with dilute acids, a yellowish solid was produced, identified as the acridone. In cold concentrated sulphuric acid it gave a purple solution, the colour disappearing on dilution. It was insoluble in alkalies.

(b) The properties of the dark orange compound m.p. 180±5° were similar to those of its isomer, but in every case the solubility in the various solvents was greater. With concentrated sulphuric acid, the colour produced was much bluer than with the light orange compound.

It has been shown by further experiments, discussed in the theoretical section, that the compound

m.p. 180-5° is 5:8-dichloro-2:3-benzacridine and that m.p. 231-2° the 5:6-dichloro isomer.

In a repeat experiment, some phosphorus pentachloride was added to the phosphorus oxychloride, and the mixture, as before, refluxed for two hours. On pouring into the ice, chloroform, ammonia mixture, however, a deep-red colour was produced in the chloroform and on working up the experiment a deep red solid was obtained, in contrast to the orange solid obtained using phosphorus oxychloride alone as cyclizing agent. The red solid was chromatographed using alumina as adsorbent and a 50% benzene-light petroleum (60-80°) mixture as solvent. A red band passed quickly down the column and was collected as an orange, fluorescent solution. On reducing the volume of the solution, a deep red solid crystallised which after recrystallising from light petroleum yielded long red rods, m.p. 262-3°. This compound analysed as follows -

Found: C - 61.05; H - 2.65; N - 3.9.

$C_{17}H_8NCl_3$ requires C - 61.35, H - 2.4, N - 4.2.

It thus appeared to be a trichlorobenzacridine, giving a deep blue colour in concentrated sulphuric acid, in contrast to the purple colour obtained with the dichloro compounds. This compound has since been identified as 1:5:8-trichloro-2:3-benzacridine, as

has been discussed in the theoretical section of this thesis.

Following the red band of the chromatogram, a light orange band passed down the column and yielded some 5:6-dichloro-2:3-benzacridine. A deeper orange band was eluted with benzene and proved to be some of the 5:8-dichloro isomer.

6-chloro-2:3-benzacridone.

5:6-dichloro-2:3-benzacridine was heated on the water bath for half-an-hour with 2 $\bar{N}$-sulphuric acid. After a few minutes a purple colour was produced but this soon disappeared, leaving a yellowish-orange solid. This was filtered, washed and recrystallised several times from alcohol, in which it gave a bright green fluorescence, m.p. $>360^{\circ}$.

(Found: C - 72.4; H - 3.4; ~~N~~

$C_{17}H_{10}NOCl$ - C - 73.0
H - 3.6
N - 5.02)

6-chloro-2:3-benzacridone is soluble in concentrated sulphuric acid, giving a deep purple solution, but is insoluble in all dilute acids.

As is usual with acridones, it is soluble in alcohol, but insoluble in ether and light petroleum. It is very sparingly soluble in benzene, giving a yellow solution with a blue-green fluorescence.

8-Chloro-2:3-benzacridone.

5:8-dichloro-2:3-benzacridine was heated on the water-bath for half-an-hour with 2 N-sulphuric acid. The yellow-orange solid was then filtered and re-crystallised several times from alcohol, the solution having a bright green fluorescence, m.p. 312°

(Found: ~~C~~ ~~H~~ N - 4.2

$C_{17}H_{10}NOCl$ requires C - 73.0
H - 3.6
N - 5.02.

The properties of 8-chloro-2:3-benzacridone are similar to those of the 6-chloro isomer.

3-(p-chloro-anilino)-2-naphthoic acid.

(cf. Ullmann, Ann., 1907, 355, 340.
Bachmann, J. Org. Chem., 1948, 13, 89.)

3-chloro-2-naphthoic acid (5 g.), p-chloro-aniline (3.25 g.), anhydrous potassium carbonate (3.75 g.), copper powder (.15 g.), a trace of potassium iodide and amyl alcohol were mixed and refluxed for six hours in an oil bath at 150°. On cooling a greenish solid separated. This was filtered off, washed with acetone, extracted with dilute sodium carbonate and the solution acidified with hydrochloric acid. A pale yellow solid melting at 220° separated in small amount and was identified as 3-hydroxy-2-naphthoic acid.

The amyl alcohol was removed from the filtrate by steam distillation, leaving a black, oily residue. This oil was extracted with dilute potassium carbonate solution and the hot extract acidified with acetic acid. The bright yellow solid which separated was filtered off and the filtrate made acid with hydrochloric acid. A slight opalescence was obtained.

The bright yellow material was recrystallised successively from aqueous alcohol and benzene as needles, m.p. - 245°, yield - 4.5 gms., 60% of theory. Analysis of this compound agrees with its formulation as 3-(p-chloro-anilino)-2-naphthoic acid.

(Found: C - 69.05; H - 4.55; N - 4.5;

$C_{17}H_{12}O_2N$ Cl requires C - 68.7
H - 4.05
N - 4.7.)

The slightly high C and H values is probably due to a trace of benzene.

The properties of 3-(p-chloro-anilino)-2-naphthoic acid are similar to those of the m-isomer already described.

5:7-dichloro-2:3-benzacridine.

(cf. Bachmann, J. Org. Chem. 1948, 13, 89.

3-(p-chloroanilino)-2-naphthoic acid (5 g.) was added to phosphorous oxychloride (40 c.c.) and the mixture refluxed for two hours in an oil bath at 150°. The solution became dark purple in colour and, after distilling off the phosphorous oxychloride a dark purple, oily residue was left. This was carefully added, with stirring, to a mixture of ice, concentrated ammonia and chloroform, the acridine dissolving in the chloroform to give a brown solution with a green fluorescence. The chloroform layer was separated, washed, dried over anhydrous sodium sulphate and the chloroform removed by distillation. An orange solid remained, which, after several crystallisations from benzene, melted at 227-228° with decomposition. After drying for six hours in vacuo over phosphorus pentoxide, the melting point rose to 239-240° (d). The analytical figures for this compound agree with calculated values for 5:7-dichloro-2:3-benzacridine.

(Found: C - 68.95; H - 2.9; N - 4.80.

$C_{17}H_9N\,Cl_2$ requires C - 68.45
H - 3.0
N - 4.70.)

5:7-dichloro-2:3-benzacridine is very soluble in cold ether and benzene, yielding yellow solutions with a bright green fluorescence. It is sparingly soluble in hot alcohol giving an orange solution with a green fluorescence. On warming with dilute acids, it is converted to the corresponding acridone. It dissolves in cold concentrated sulphuric acid, producing a deep purplish-blue colour which disappears on dilution.

In a repeat experiment insufficient ice was used when decomposing the excess phosphorus oxychloride and the temperature of the mixture rose. As is usual in such cases, some acridone, m.p.>360°, was produced. In an attempt to reconvert this to the 5-chloro-acridine, it was refluxed with a mixture of phosphorus oxychloride and phosphorus pentachloride for six hours in an oil bath at 150°. The solution became first purple and then dark reddish-brown in colour. The phosphorus oxychloride was distilled off and the residue worked up as already described. A deep red solid was obtained which crystallised from benzene as red needles, m.p. 259-60°. A mixed m.p. with an analysed specimen of 5:7-dichloro-2:3-benzacridine was depressed. Analysis suggested that it was a trichloro benzacridine.

(Found: C - 60.4; H - 2.25; N - 3.8.

$C_{17}H_8N\,Cl_3$, $\frac{1}{4}\,H_2O$ requires C - 60.5
H - 2.5
N - 4.2.)

This suggestion has been discussed in the theoretical section of this thesis.

This compound is very soluble in cold ether and benzene and sparingly soluble in cold alcohol, giving a reddish-orange solution with a green fluorescence. With concentrated sulphuric acid a bright blue solution is obtained, which, on dilution with water, becomes first purple and then colourless. On warming with dilute acids the red colour of the solid is discharged and an orange solid is formed melting above 360° which is probably an acridone.

7-chloro-2:3-benzacridone.

5:7-dichloro-2:3-benzacridine was heated on the water bath with 2 $\bar{N}$ sulphuric acid for half-an-hour. The supernatant liquid became purple while the solid remained light orange in colour. This solid was filtered off, washed with water, and recrystallised several times from a large volume of alcohol, in which it dissolved to give a yellow solution with a bright green fluorescence. 7-chloro-2:3-benzacridone crystallised as orange needles. M.p.>360°. It analysed as follows:-

Found: C - 70.5; H - 3.4; N - 4.3;

$C_{17}H_{10}NOCl$, $\frac{1}{2}$ H_2O requires C - 70.7
H - 3.8
N - 4.8.

7-chloro-2:3-benzacridone is sparingly soluble in ether and benzene, giving a yellow solution with a green fluorescence. With concentrated sulphuric acid a deep bluish-red solution is obtained which, on dilution, becomes orange in colour.

3-(o-chloro-anilino)-2-naphthoic acid.

(cf. Ullmann, Ann. 1907, 355, 340.
Bachmann, J. Org. Chem., 1948, 13, 89.)

3-chloro-2-naphthoic acid (5 g.), o-chloro-aniline (3.25 g.), copper bronze (.15 g.), a trace of potassium iodide and amyl alcohol (40 c.c.) were mixed and refluxed in an oil bath for six hours at 150°. The mixture became very dark and on cooling a small amount of solid separated. This was filtered off, washed with acetone, extracted with 2 $\bar{N}$ sodium carbonate and acidified with hydrochloric acid, yielding, as in the experiments with the m- and p- chloro-anilines, some 3-hydroxy-2-naphthoic acid. The amyl alcohol filtrate was steam-distilled, the black oily residue extracted with potassium carbonate, and, while still hot, acidified with acetic acid. The canary yellow solid which separated was filtered off. Acidification of the filtrate with hydrochloric acid precipitated a small amount of pale yellow solid identified as in previous experiments as 3-chloro-2-naphthoic acid. The canary yellow solid — 3-(o-chloroanilino)-2-naphthoic acid — after several crystallisations from alcohol, melted at 230°.

Yield - 4½ gms. (60% of theory).

(Found: C - 66.3; H - 3.8; N - 4.85.

$C_{17}H_{12}O_2NCl$, $\frac{1}{2}$ H_2O requires C - 66.55
H - 4.2
N - 4.6.)

The properties of 3-(o-chloroanilino)-2-naphthoic acid are similar to those of the m- and p-isomers already described.

5:9-dichloro-2:3-benzacridine.

3-(o-chloro-anilino)-2-naphthoic acid (6 g.) was added to phosphorus oxychloride (60 c.c.) and the mixture refluxed for two hours in an oil bath at 150°. The solution became dark purple in colour and on distilling off the phosphorus oxychloride a dark-purple oily residue remained. This was poured into a mixture of ice, ammonia and chloroform, the base dissolving in the chloroform to give an orange-red solution with a green fluorescence. The chloroform layer was separated, washed, dried over anhydrous sodium sulphate and the solvent distilled off. The deep orange-red solid residue — 5:9-dichloro-2:3-benzacridine — was crystallised from dry benzene as rods, m.p. 203°; yield - 4 gms. (80% of theory).

(Found: C - 66.7; H - 2.80; N - 5.0.

$C_{17}H_9NCl_2$, $\frac{1}{2}$ H_2O requires C - 66.45
H - 3.2
N - 4.6.)

The properties of 5:9-dichloro-2:3-benzacridine are similar to those of the 5:7-dichloro isomer.

9-chloro-2:3-benzacridone.

5:9-dichloro-2:3-benzacridine was heated with 2 $\bar{N}$-hydrochloric acid on the water-bath for half-an-hour. The red colour of the acridine disappeared and an orange solid was formed. This was filtered, washed and recrystallised from alcohol, the solution being coloured yellow with a green fluorescence. After several crystallisations from benzene, 9-chloro-2:3-benzacridone was obtained as yellow crystals, m.p. 271-2°.

(Found: C - 72.2; H - 3.6; N - 4.8

$C_{17}H_9NOCl$, $\frac{1}{8}$ H_2O requires C - 72.4
H - 3.6
N - 5.0)

9-chloro-2:3-benzacridone is soluble in ether and benzene, giving yellow solutions with a green fluorescence, but is insoluble in light petroleum. It dissolves in concentrated sulphuric acid, giving a reddish-purple solution, which, on dilution, becomes yellow in colour.

4-chloro-2-(1'-bromo-β-naphthylamino)-benzoic acid.

First Method - Attempted preparation from 1-bromo-β-naphthylamine and 2:4-dichloro-benzoic acid.

(cf. Dobson, Hutchison and Kermack, J.C.S. 1948, 123.)

(a) 1-bromo-β-naphthylamine (6.6 g.), 2:4 dichloro-benzoic acid (5.7 g.), anhydrous potassium carbonate (4.06 g.), copper bronze (0.1 g.), a trace of potassium iodide and amyl alcohol (50 c.c.) were mixed and refluxed in an oil bath at 160° for six hours. The solution became green and then, after a few hours, black. On cooling, a brownish solid separated, which was washed with amyl alcohol and acetone. On extraction with sodium carbonate, the bulk of the material was insoluble and was filtered off. The hot carbonate extract on acidification with acetic acid gave no precipitate, but on the addition of hydrochloric acid a very small amount of white solid separated.

The amyl alcohol was removed from the filtrate by steam-distillation, a black oily residue being left. On boiling with potassium carbonate solution, this oil did not appear to dissolve completely, but formed a suspension which was difficult to filter. After several filtrations through a fluted filter-paper, the solution, which still remained opalescent,

was acidified with acetic acid; a small amount of pinkish-brown, oily solid separated. This was filtered off and hydrochloric acid added to the filtrate. The white, curdy solid, which was precipitated in quantity, was purified by re-extracting with sodium carbonate, filtering and re-acidifying. It was finally crystallised from dilute acetic acid as white needles m.p. 241-3°, identical with an authentic specimen of p-chloro-benzoic acid. This result has been discussed in an earlier section of this thesis.

(b) The experiment was repeated, but the time of heating was reduced to two hours. A similar result was obtained.

(cf. Goldberg and Kelly, J.C.S., 1946, 102.)

(c) The experiment was carried out using iso-propyl-alcohol as solvent in place of amyl alcohol. The solution again became green, but no blackening was observed. On cooling a greenish residue separated. This was filtered, washed with acetone, extracted with 2 N-sodium carbonate and acidified with dilute hydrochloric acid. A curdy white precipitate, which after several crystallisations from dilute acetic acid melted at 241-3°, separated and was identified as p-chloro-benzoic acid.

After removing the iso-propyl-alcohol from the

filtrate by steam distillation, a black oil remained. The oil was thoroughly extracted with potassium carbonate and the solution acidified with acetic acid. The purplish solid which separated was filtered off. Addition of hydrochloric acid to the filtrate caused more p-chloro-benzoic acid to separate. The purplish solid ($\frac{1}{2}$ gm.) was recrystallised several times from aqueous alcohol and benzene and was finally obtained as pale yellow rectangular plates, softening at 262° and melting at 272°. Yield - 2 gm.

(Found: C - 53.5; H - 3.0; N - 3.5.

$C_{17}H_{11}NO_2Cl\ Br$, $\frac{1}{4}\ H_2O$ requires C - 53.5
H - 3.0
N - 3.7.)

This compound was therefore characterised as 4-chloro-2-(1'-bromo-β-naphthylamino)-benzoic acid.

The bulk of the material in this experiment remained as tar, insoluble in potassium carbonate. Some unchanged 1-bromo-β-naphthylamine was distilled over in the steam.

4-chloro-2-(1'-bromo-β-naphthylamino)-benzoic acid is soluble in alcohol, ether, benzene and dilute ammonia. With dilute sodium hydroxide, a white, sparingly soluble sodium salt is formed. The acid is also soluble in glacial acetic acid and concentrated sulphuric acid, but is reprecipitated from these solutions on dilution with water.

4-chloro-2-(β-naphthylamino)-benzoic acid.

(cf. Dobson, Hutchison and Kermack, J.C.S., 1948, 123.)

β-naphthylamine (5.7 g.), potassium 2:4 dichloro benzoate (9.2 g.), amyl alcohol (30 c.c.), copper bronze (.1 g.) and a trace of potassium iodide were mixed and refluxed in an oil bath at 150° for six hours. The mixture, which became dark purple in colour, was cooled and the dark purple oily solid which separated filtered off. On washing the residue thoroughly with acetone, all the purple material dissolved, leaving behind a small amount of greenish-white material. This was extracted with sodium carbonate and the solution acidified with hydrochloric acid, when a white solid m.p. 220° was precipitated and identified as p-chloro-benzoic acid, a mixed melting point with an authentic specimen of this acid showing no depression.

The amyl alcohol filtrate and the acetone washings were steam distilled, leaving a black tarry residue. This was thoroughly extracted with dilute ammonia, a considerable portion being insoluble. On extracting the insoluble material with dilute hydrochloric acid and making the solution alkaline with dilute caustic soda, a pinkish solid separated, which recrystallised from hot water in glistening plates

m.p. 112°, and was identified as unchanged β-naphthylamine. The ammonia extract was acidified in the hot with acetic acid, a purplish solid being precipitated. This precipitate was treated with charcoal in aqueous alcohol solution, and further crystallised from benzene as pale yellow needles m.p. 231-2°. This compound was assumed to be 4-chloro-2-(β-naphthylamino)-benzoic acid which Dobson, Hutchison and Kermack describe as pale violet needles m.p. 272°. This quoted m.p. is a typographical error for 227°.

A further experiment was carried out using isopropyl alcohol as solvent, but no reaction took place, the original materials being recovered.

4-chloro-2-(1^1-bromo-β-naphthylamino)-benzoic acid.

Second Method - Bromination of 4-chloro-2-(β-naphthylamino)-benzoic acid.

(cf. Lellmann and Schmidt, Ber., 1887, 20, 3154.
Franzen and Stäuble, J. Pr. Chem., 1921, 101, 59.)

4-chloro-2-(β-naphthylamino)-benzoic acid (10 g.) was dissolved in cold glacial acetic acid and bromine (5.35 g.), also dissolved in acetic acid, was slowly added with stirring. After a few minutes a pale yellow solid began to separate. After standing for half-an-hour, the solid was filtered off, washed and crystallised several times from alcohol, giving pale yellow rectangular plates which softened at 262° and melted at 272°. A mixed melting point with a specimen of 4-chloro-2-(1^1-bromo-β-naphthylamino)-benzoic acid, prepared by an Ullmann condensation carried out on 1-bromo-β-naphthylamine and 2:4 dichloro-benzoic acid as already described, was not depressed. On adding water to the acetic acid filtrate, a small amount of similar material was obtained. Yield 10 gm. (79% of theory).

During an experiment carried out on a large scale, the bromine, dissolved in glacial acetic acid, was added to a warm solution of 4-chloro-2-(β-naphthylamino)-benzoic acid in the same solvent. In

this experiment a bright yellow solid separated, m.p. approximately 270°, which was much less soluble in alcohol and benzene than the bromo compound obtained in the experiment already described. It was also insoluble in dilute acids and with dilute sodium hydroxide gave a white, sparingly soluble sodium salt. After several crystallisations from alcohol the melting point was raised to 278°. This compound gave the following analytical results.

(Found: C - 47.1; H - 2.6; N - 3.5.

$C_{17}H_{11}NO_2Cl\ Br$. requires C - 54.2
H - 2.9
N - 3.7.

$C_{17}H_{10}NO_2Cl\ Br_2$ requires C - 44.8
H - 2.2
N - 3.1.)

These figures suggest that this may be a mixture of the desired mono-bromo compound and a dibromo analogue. The formulation of the latter as 4-chloro-2-(1^1:6^1-dibromo-β-naphthylamino)-benzoic acid has been discussed in an earlier section of this thesis.

1-bromo-5:8-dichloro-2:3-benzacridine.

4-chloro-(1[1]-bromo-β-naphthylamino)-benzoic acid (2 g.) was dissolved in phosphorus oxychloride (20 c.c.) and the mixture refluxed in an oil bath at 150° for two hours. The solution became dark purple, but on cooling the colour changed to dark green. The oil remaining after distilling off the phosphorus oxychloride was slowly stirred into a mixture of ice, chloroform and ammonia, when the chloroform layer became bright scarlet in colour and a green fluorescence was observed. The chloroform layer was separated, washed with water, dried over anhydrous sodium sulphate and the solvent distilled off. A scarlet solid remained which was very soluble in benzene, giving a red solution with a brilliant orange fluorescence. On reducing the volume, a pink solid separated, melting at 220-30°. Further crystallisations from benzene and ether did not improve the melting point or lessen the intensity of the colour. It was found that purification was best effected by triturating the pink solid with benzene in the cold several times. The benzene was coloured a deep red, while the residual solid became a paler pink. This solid was dissolved in benzene, the solution treated several times with charcoal and the solid precipitated by the addition of ether. It was then crystallised

several times from a mixture of benzene and ether, very pale pink crystals being obtained, m.p. 241-2°. The analytical results for this compound are as follows:

Found: C - 54.3; H - 1.9; N - 3.4.

$C_{17}H_8NCl_2Br$ requires C - 54.1
H - 2.1
N - 3.7.

It was thus concluded that the pale pink solid was 1-bromo-5:8-dichloro-2:3-benzacridine.

This compound is soluble in benzene, ether and alcohol, giving colourless, non-fluorescent solutions, but only very sparingly soluble in light petroleum. On heating with dilute hydrochloric acid a yellowish solid is obtained, melting over 360°, which has been identified as the corresponding acridone.

The benzene was now distilled off from the mother liquors containing the dark red material. A dark red solid remained, melting at approximately 170-190°. A portion of this material, on extraction with alcohol, gave a red fluorescent solution, but on boiling for a few minutes, the red colour was discharged, the solution becoming yellow with a brilliant green fluorescence. The same effect was obtained on adding charcoal to an alcohol solution in the cold. On reducing the volume of the solution, a yellow solid

separated which, after several crystallisations from alcohol, melted at 349-50°. It gave the following analytical results:-

Found: C - 64.1; H - 2.6; N - 4.3.

These figures do not agree with the values calculated for a bromochloro acridone, but agree with those for a dichloro acridone.

$C_{17}H_9NOCl\,Br$ requires C - 56.9
H - 2.5
N - 3.9.

$C_{17}H_9NOCl_2$ requires C - 64.95
H - 2.9
N - 4.5.

This material dissolved in concentrated sulphuric acid, giving a purplish-red colour which was discharged on dilution. It was insoluble in dilute acids, alkalis, ether and benzene, but soluble in alcohol, giving a yellow solution with a bright green fluorescence. Several crystallisations of the dark red solid from benzene did not sharpen the melting point. It was therefore decided to chromatograph the mixture.

No separation was obtained on passing a solution of the red material in benzene through an alumina column suspended in benzene. When the chromatograph experiment was repeated in another alumina column,

using a 50% benzene-light petroleum (60-80°) mixture as solvent, some separation was effected. A red band passed quickly through the column and was collected as a yellow-orange solution with a green fluorescence. The yellow band which remained adsorbed on the alumina was washed through with benzene, a yellow solution with a bright green fluorescence being collected. On reducing the volume of the first yellow-orange washings, deep-red, rod-shaped crystals separated. After several crystallisations from light petroleum (40-60°), these crystals melted sharply at 264-5°. The following analytical result was obtained -

Found: N - 4.3.

$C_{17}H_8NCl_3$ requires N - 4.2.

The compound therefore appears to be a trichlorobenzacridine. Its identification as 1:5:8-trichloro-2:3-benzacridine has been discussed in the theoretical section of this thesis.

The acridone m.p. 349-50° already described has also been characterised as 1:8-dichloro-2:3-benzacridone.

1-bromo-8-chloro-2:3-benzacridone.

1-bromo-5:8-dichloro-2:3-benzacridone was heated with 2 $\bar{N}$-hydrochloric acid on the water bath for half an hour. A buff coloured solid was obtained which was filtered off, washed and dissolved in hot alcohol giving a yellow solution with only a very slight green fluorescence. On cooling 1-bromo-8-chloro-2:3-benzacridone crystallised as buff-coloured needles m.p. $> 360^{\circ}$. It analysed as follows:

Found: C - 56.6; H - 2.6; N - 4.2.

$C_{17}H_9NOCl\,Br$ requires C - 56.9
H - 2.5
N - 3.9.

1-bromo-8-chloro-2:3-benzacridone is insoluble in ether and benzene and only sparingly soluble in alcohol, the solution showing a faint green fluorescence. With concentrated sulphuric acid it gives only a pale yellow colouration in contrast to the purplish-red colour produced by 1:8-dichloro-2:3-benzacridone.

Attempts to eliminate the bromine atom from 1-bromo-5:8-dichloro-2:3-benzacridine.

(cf. Franzen and Stäuble, J. Pr. Chem., 1921, 101, 59.)

(a) 1-bromo-5:8-dichloro-2:3-benzacridine ($\frac{1}{2}$ gm.) stannous chloride (.23 g.), concentrated hydrochloric acid (.8 c.c.) and alcohol (2 c.c.) were mixed and heated on the water-bath for five hours. After a few minutes the pink colour of the acridine was replaced by the buff colour of the corresponding acridone, but no further change was observed. The mixture was poured into water, the buff solid filtered off and recrystallised from alcohol, m.p. $> 360^{\circ}$.

The alcohol solution had only a very faint fluorescence and a mixed melting point with an analysed specimen of 1-bromo-8-chloro-2:3-benzacridone was not depressed. If the bromine had been removed to give 8-chloro-2:3-benzacridone, a brilliant green fluorescence in the alcohol would have been observed.

(b) The experiment was repeated using a large volume of alcohol to keep the acridone in solution. Again no change was observed and the bromo-acridone was recovered.

(c) An experiment was carried out in which the bromo-acridone was dissolved in glacial acetic acid

before adding the stannous chloride and concentrated hydrochloric acid. Again no change was observed, the bromo-acridone being recovered unchanged.

(d) 1-bromo-8-chloro-2:3-benzacridone ($\frac{1}{2}$ g.) was added to a suspension of red phosphorus (1 g.) in hydriodic acid (10 c.c.), and the mixture heated on the water-bath for three hours. It was then poured into water, the dark red solid filtered off, washed with water and extracted with alcohol. A reddish-orange solution was obtained from which, on reducing the volume, an orange solid crystallised melting at approximately 170°. This was extracted with acetone, the solution treated with charcoal, and the volume reduced to yield a pale yellow crystalline solid. After several recrystallisations from acetone, this solid melted at 212-13°. The analytical results are as follows:-

Found: C - 58.8; H - 2.6;

$C_{17}H_9NCl\,Br$, $\frac{1}{4}\,H_2O$ requires C - 58.8
H - 2.7

As discussed earlier, this may be 1-bromo-8-chloro-2:3-benzacridine, 1-bromo-8-chloro-2:3-benzacridone having been merely reduced to the corresponding acridine without the removal of the bromine atom.

This compound is soluble in alcohol and benzene.

It is insoluble in dilute alkalis but dissolves in dilute acids giving a yellow solution.

The experiment was repeated, a trace of copper bronze being added as catalyst. The dark red solid obtained on pouring the mixture into water was filtered off and extracted with acetone. A yellow solution was obtained with a green fluorescence, but on charcoaling, the fluorescence disappeared, and on reducing the volume of the solution, some of the original bromo-acridone crystallised out. A further reduction in volume yielded a pale yellow solid m.p. 210° identical with that obtained in the last experiment.

As already discussed, the bromine may have been removed to a very slight extent, giving a small amount of 8-chloro-2:3-benzacridone which would account for the appearance of the fluorescence.

Attempts to brominate 6-chloro-2:3-benzacridone.

(a) 6-chloro-2:3-benzacridone ($\frac{1}{2}$ g.) was dissolved in glacial acetic acid (20 c.c.), a solution of bromine (.24 c.c.) in the same solvent was slowly stirred in, and the light orange mixture heated on the water-bath for three hours. Some of the glacial acetic acid was then distilled off under reduced pressure, when an orange solid crystallised out, m.p. $> 360^{\circ}$, which, on dissolving in alcohol, produced a bright green fluorescence. Owing to the high melting point of the acridone, the disappearance of the fluorescence would be the main indication of the introduction of a bromine into the acridine nucleus. If a trace of the bromo acridone were formed, it would not therefore be easily detected.

(b) The experiment was repeated using excess bromine, nitrobenzene as solvent, and a trace of iodine as catalyst. On removing the nitrobenzene by steam distillation, an orange solid, m.p. $> 360^{\circ}$, was obtained, which gave a brilliant green fluorescence in alcohol, and was assumed to be the original acridone.

4-Chloro-2-(1'-chloro-β-naphthylamino)-benzoic acid.

1-chloro-β-naphthylamine (5 g.), 2:4-dichlorobenzoic acid (5.4 g.), anhydrous potassium carbonate (3.88 g.), copper bronze (.1 g.), a trace of potassium iodide, and isopropyl alcohol (50 c.c.) were mixed and refluxed for six hours in an oil-bath at 130°. The solution became greenish-blue in colour, and on cooling, the greenish-white solid which separated was filtered, washed with acetone, and extracted with hot dilute ammonium hydroxide. On acidifying the extract with hydrochloric acid, a copious white precipitate formed, which on crystallising from dilute acetic acid was obtained as needles m.p. identical with p-chlorobenzoic acid. Yield - 3g.

The isopropyl-alcohol filtrate and acetone washings were steam distilled. A white solid came over in the steam m.p. 56°, identified as unchanged 1-chloro-β-naphthylamine. The black oily residue which remained was first extracted with dilute hydrochloric acid. On making the extract alkaline, a pink solid separated, which on crystallising from aqueous alcohol was obtained as white needled m.p. 56°, identical with the original 1-chloro-β-naphthylamine. Yield - 3½g.

The oily material, insoluble in dilute hydro-

chloric acid, was extracted with dilute ammonia. Most of it dissolved, leaving only a small amount of black oil. On acidifying the hot extract with acetic acid, a yellow solid separated. This was filtered off, and the filtrate made acid to hydrochloric acid. A further quantity of white solid precipitated, identified as p-chlorobenzoic acid.

The yellow solid, precipitated by the acetic acid, crystallised from aqueous alcohol as rectangular tetrahedra, and from benzene as long needles, which softened at 230° and melted at 255°. After drying at 80° over phosphorus pentoxide for three hours, this compound, assumed to be 4-chloro-2-(1'-chloro-β-naphthylamino)-benzoic acid, was found to melt from 235-45°. It analysed as follows -

Found: C - 61.5; H - 3.25; N - 4.4.

$C_{17}H_{11}NCl_2O_2$ requires C - 61.45
H - 3.3
N - 4.2.

This result has been discussed earlier in this thesis.

1:5:8-trichloro-2:3-benzacridine.

4-Chloro-2-(1^1-chloro-β-naphthylamino)-benzoic acid (1 g.) was added to phosphorus oxychloride (10 c.c.) and the mixture refluxed for two hours in an oil-bath at 150°. The solution became deep red, and finally purplish-brown in colour. The excess oxychloride was distilled off, and the residue poured in a mixture of ice, chloroform and concentrated ammonia. The chloroform layer became deep red in colour and an orange-green fluorescence was observed. This layer was separated, washed, dried over anhydrous sodium sulphate, and the chloroform distilled off. A deep red solid was obtained which after four crystallisations from benzene and light petroleum (60-80°) still melted from 190-230°. It was thus dissolved in a 50% benzene-light petroleum (60-80°) mixture, and passed into an alumina column suspended in the same solvent. A deep red band passed quickly through the column, leaving a yellow band strongly adsorbed on the alumina. The red band was collected as a yellow-orange fluorescent solution which, on being reduced in volume, yielded a deep red solid, m.p. 257-9°. On recrystallising from light petroleum (40-60°), 1:5:8-trichloro-2:3-benzacridine was obtained as long red rods m.p. 262-3° which analysed as follows -

Analytical values for C & H not yet forward.

Yield - 0.6g.

This compound dissolves in alcohol, ether and benzene, giving red fluorescent solutions, and in light petroleum, giving yellow-orange fluorescent solutions. It is soluble in concentrated sulphuric acid, a deep blue colour being produced.

The yellow band adsorbed on the alumina was washed through with benzene. A yellow, non-fluorescent solution was collected, from which, on reducing the volume, a small amount of an orange-pink solid crystallised m.p. 230-6°. Crystallisation from light petroleum (40-60°) yielded pink needles, m.p. 238°. It analysed as follows -

Found: C - 59.7; H - 2.3

$C_{17}H_8NCl_3$, $\frac{1}{2}H_2O$ requires C - 59.7
H - 2.6

The formulation of this compound as an isomeric trichloro-benzacridine has been discussed in the theoretical section of this thesis.

The chlorination of 5:6-dichloro-2:3-benzacridine with phosphorus pentachloride.

(cf. Goodall and Kermack, J.C.S., 1936, 1163.)

Three experiments were carried out using one, two and three molecules of phosphorus pentachloride respectively -

(a) A mixture of 5:6-dichloro-2:3-benzacridine (½ g.), phosphorus pentachloride (.35 g.) and phosphorus oxychloride (5 c.c.) was refluxed in an oil-bath at 150° for three hours. The purple colour produced at the beginning did not change as in the corresponding experiment with the 5:8-isomer. After distilling off the excess phosphorus oxychloride, the residue was poured into a mixture of ice, chloroform and ammonia when an orange colour was produced in the chloroform layer. After washing and drying the chloroform layer, and removing the solvent, an orange solid was obtained (.35 g.) which, on crystallising from benzene, melted at 230-2° and proved to be the original 5:6-dichloro-2:3-benzacridine.

(b) The experiment was repeated using twice the amount of phosphorus pentachloride. This time, the chloroform layer remained almost colourless and a pink solid was obtained, which, after several crystallisations from light petroleum, yielded pale-pink

rectangular tetrahedra, which turned a deep-red colour at 175-180° and melted at 183°. Yield - .2 g. This was the only product isolated in the reaction and gave the following analytical results -

Found: C - 50.15; H - 2.1

$C_{17}H_6NCl_5$	requires	C - 50.8
		H - 1.5
		N - 3.5
$C_{17}H_8NCl_3.Cl_2$	requires	C - 50.55
		H - 2.0
		N - 3.5.

The formulation of this compound as a pentachlorobenzacridine or as a perchloride of a trichlorobenzacridine has been discussed in the theoretical section of this thesis.

It is soluble in benzene, ether alcohol giving pinkish, non-fluorescent solutions. It dissolves in concentrated sulphuric acid, giving a deep blue solution which turns pink on dilution.

(c) In a similar experiment using three molecules of phosphorus pentachloride, a deep-red colour was produced in the chloroform layer, and on removing the solvent a deep red solid remained which was dissolved in light petroleum and passed into an alumina column in the same solvent. A deep red band passed quickly down the column and was collected as a deep red solution. On reducing the volume of this

solution, a deep purple-red solid was obtained which after several crystallisations from the same solvent melted at 185°. The amount obtained pure, however, was insufficient for analysis.

On washing the column with benzene, a pinkish solid was obtained, melting from approximately 160-190°, but all attempts to purify this material by crystallisation have proved unsuccessful.

The chlorination of 5:8-dichloro-2:3-benzacridine using phosphorus pentachloride.

(cf. Goodall and Kermack, J.C.S., 1936, 1163.)

Three experiments were carried out using one, two and three molecules of phosphorus pentachloride respectively.

(a) 5:8-dichloro-2:3-benzacridine (m.p. 180-5°) (5 g.), phosphorus pentachloride (.35 g.), and phosphorus oxychloride (5 c.c.) were mixed and refluxed in an oil-bath at 150° for two hours. The mixture, at first purple in colour, became reddish-brown, and on cooling, dark green. The excess phosphorus oxychloride was distilled off and the oily residue poured into a mixture of ice, chloroform and concentrated ammonia. A reddish-orange colour was produced in the chloroform, which was separated, washed, dried over sodium sulphate and the solvent distilled off. A reddish-orange solid remained which melted at approximately 160-190°. This material was dissolved in a 50% benzene-light petroleum (60-80°) mixture and passed into an alumina column in the same solvent. A deep red band passed quickly down the column, while an orange band remained strongly adsorbed at the top. After all the red material had been washed through, the column was extruded and the orange-band eluted

with benzene. On reducing the volume of the extract, a reddish-orange solid (.2 g.) was obtained, m.p. 178-180°, identical with some of the original 5:8-dichloro-2:3-benzacridine.

On distilling off the solvent from the orange solution containing the red material, a rose-red solid remained which after several crystallisations from benzene and light petroleum melted at 240-44°. No further purification could be effected by crystallisation. When mixed with a sample of 1:5:8-trichloro-2:3-benzacridine (m.p. 264-5°) the melting point was not depressed, and on carrying out a micro-melting point on this material, crystals were observed to sublime which had the characteristic rod-shaped form of the 1:5:8-trichloro- compound, and which did not melt completely until 259°. This compound was therefore most probably impure 1:5:8-trichloro-2:3-benzacridine, but the small quantity obtained prevented further purification.

(b) A similar experiment was carried out using two molecules of phosphorus pentachloride (.7 g.) and worked up in a similar manner to that described above. On pouring the oily residue left after removing the excess phosphorus oxychloride, into a mixture of ice, chloroform and ammonia, a deep-red colour was produced in the chloroform. The chloroform layer was

separated, washed, dried and the solvent removed. A rose-red solid m.p. 240-44° was obtained which could not be further purified by crystallisation. It was therefore dissolved in light-petroleum (60-80°) and passed into an alumina column in the same solvent. No separation appeared to take place, the red band passing quickly down the column and being collected as an orange fluorescent solution. Six 100 c.c. fractions were collected, and reduced in volume. The first two fractions yielded deep-red, rod-shaped crystals which after crystallising from the same solvent melted at 262-3° and did not depress the melting point of an authentic specimen of 1:5:8-trichloro-2:3-benzacridine, and gave the following analytical results -

Found: C - 60.9; H - 2.8

$C_{17}H_9NCl_3$ requires C - 61.35
H - 2.4

5:8-dichloro-2:3-benzacridine had thus chlorinated in the one position. The next four fractions obtained from the chromatogram also yielded red solids which were lighter in colour than the 1:5:8-trichloro compound and which melted approximately from 200-240°. This material, obviously a mixture of different compounds, was not further purified by crystallisation. Only a few mg. of the 1:5:8-trichloro-2:3-benzacridine

was obtained pure, the bulk of the material (.2 g.) being the mixture of compounds which have not been further purified.

(c) The experiment was repeated using three molecules (1.05 g.) of phosphorus pentachloride. This time, the chloroform layer had only a faint reddish-brown colouration, and on removing the solvent, after washing and drying the solution, a pink solid remained. This was triturated with cold benzene, giving a red solution and leaving an almost white solid. On removing the solvent from the benzene extract, a small amount of red oil remained which failed to crystallise. The pale pink solid was crystallised several times from light-petroleum (60-80°) and was finally obtained as pale pink needles which melted to a deep-red liquid at 205°, yield .2 g.

This compound gave the following analytical results -

Found: C - 50.05; H - 2.0; N - 3.2

$C_{17}H_6NCl_5$, $\frac{1}{2}$ H_2O	requires	C - 49.7
		H - 1.7
		N - 3.4
$C_{17}H_8NCl_3.Cl_2$	requires	C - 50.55
		H - 2.0
		N - 3.5

Its formulation as a pentachloro-2:3-benzacridine or

as a perchloride of a trichloro-2:3-benzacridine has been discussed in the theoretical section of this thesis. It dissolves in concentrated sulphuric acid, giving a deep green solution which becomes yellowish-green on dilution.

7-chloro-5-diethylamino-ethylamino-2:3-benzacridine.

A mixture of phenol (10 g.) and diethylamino-ethylamine (1 g.) was dried at 100° under reduced pressure for three hours. 5:7-dichloro-2:3-benz-acridine (1 g.) was then added, a deep red colour being immediately produced in the phenol. The mixture was heated on the water bath for a further three hours, an orange solid gradually depositing after the first hour. After cooling, the mixture was treated with 2 N̄-sodium hydroxide, when the phenol dissolved, leaving an oily orange solid. This was filtered, washed and extracted with cold 2 N̄-acetic acid when a red fluorescent solution was obtained. The orange solid residue melted over 360° and was identified as 7-chloro-2:3-benzacridone.

On making the red acetic acid solution alkaline with 2 N̄-sodium hydroxide, an oily red solid was obtained, which dissolved in ether, giving a red solution. This solution was dried over anhydrous sodium sulphate and the ether evaporated off. A red oil was left which did not solidify on scratching or on standing in the ice chest for a few days. Various attempts to crystallise it from light petroleum were also unsuccessful. The oil was therefore redissolved in ether and an ethereal solution of oxalic acid added. A very deep red oxalate was precipitated.

On attempting to crystallise this from alcohol, an orange solid m.p. $>360^{\circ}$ was formed, identical with the corresponding 7-chloro-acridone. After crystallising the oxalate several times from dry acetone, the melting point remained constant at 140°, decomposition taking place on melting, but the solid still remained amorphous, and no crystals were seen under the microscope. On being exposed to the atmosphere for any length of time, the oxalate became sticky and appeared to be slightly hygroscopic. After drying for six hours over phosphorus pentoxide, the following analytical results were obtained.

Found: C - 50.9; H - 5.6; N - 6.7.

$C_{23}H_{24}N_3Cl$, $2C_2H_2O_4$, 4 H_2O requires C - 51.4
H - 5.7
N - 6.7.

The yield was extremely poor, only enough for analysis being obtained.

This oxalate is soluble in water, alcohol and acetone, but is insoluble in ether.

(8^1-bromo-6^1-quinolyl)-anthranilic acid.

(cf. Hutchison and Kermack, J.C.S., 1947, 678.)

A mixture of 8-bromo-6-amino-quinoline (7 g.), potassium-o-chlorobenzoate (6.1 g.), copper bronze (0.1 g.) and amyl alcohol (10 c.c.) was refluxed for six hours in an oil-bath at 150°. The amyl alcohol was then removed by steam distillation, and the solid residue extracted thoroughly with boiling 2 $\bar{N}$-potassium hydroxide. The hot alkaline solution was acidified with acetic acid, yielding a yellowish, sticky solid, which was purified by extraction with dilute ammonia and re-precipitation in the hot with dilute acetic acid. An orange solid was thus obtained which was very soluble in alcohol and which after several crystallisations from ether melted at 259°. Yield - 2½ gm.

The material which was insoluble in the 2 $\bar{N}$ potassium hydroxide was extracted with boiling 2 $\bar{N}$ hydrochloric acid. The yellow extract was basified with ammonia, when a greenish solid was precipitated. This also proved to be very soluble in alcohol, and on crystallising from ether melted at 259° and did not depress the melting point of the compound already isolated. This compound, assumed to be (8^1-bromo-6^1-quinolyl)-anthranilic acid was easily soluble in

2 $\bar{N}$ potassium hydroxide, only slightly soluble in 2 $\bar{N}$ sodium hydroxide and 2 $\bar{N}$ ammonium hydroxide, and insoluble in 10 $\bar{N}$ sodium hydroxide.

It dissolved in dilute hydrochloric, nitric, acetic and sulphuric acid and in glacial acetic acid, but was insoluble in concentrated hydrochloric acid and nitric acid.

Attempts to prepare 2-bromo-5-chloro-3:4:2^1:3^1-pyridoacridine.

(cf. Hutchison and Kermack, J.C.S., 1947, 678.)

(a) (8^1-bromo-6^1-quinolyl)-anthranilic acid (1 g.) was added to phosphorus oxychloride (5 c.c.), and the mixture refluxed for eight hours in an oil-bath at 150°. The excess phosphorus oxychloride was then distilled off and the residue triturated with 2 $\bar{N}$ sodium hydroxide. A greyish-green solid was formed which was filtered, washed and, after being thoroughly dried in a vacuum dessicator, extracted with hot dry benzene. On cooling, brownish needles, m.p. 228-30°, separated from the solution. After several crystallisations from the same solvent, yellowish needles, m.p. 225°, were obtained. Yield - .6 g. This compound analysed as follows:-

Found: C - 57.8; H - 2.85; Halides ≡ 1 mg. - 0.94

Calculated for $C_{16}H_8N_2ClBr$ - C - 55.9; H - 2.3; Halides ≡ 1 mg. - 0.965

Calculated for $C_{16}H_8N_2Cl_2$ - C - 64.2; H - 2.7; Halides ≡ 1 mg. - 0.96

Its formulation as a mixture of 2-bromo-5-chloro- and 2:5-dichloro-3:4:2^1:3^1-pyridoacridine has been discussed in the theoretical section of this thesis.

(b) A second experiment was carried out, a similar mixture being refluxed for twenty-four hours in an oil-bath at 150°. The product obtained on distilling off the phosphorus oxychloride and triturating with ice and 2 $\bar{N}$ sodium hydroxide, was filtered, washed, dried and extracted with hot, dry benzene. On reducing the volume of the extract, a light-brown solid separated which after several crystallisations from benzene was found to melt at 218-219°. This compound analysed as follows:-

Found: C - 62.55; H - 2.4; Halogen - 22.75

$C_{16}H_8N_2Cl_2$ - C - 64.2; H - 2.7; Cl - 23.75

2:5-dichloro-3:4:2^1:3^1-pyridoacridine has been prepared by Hutchison and Kermack (J.C.S., 1947, 648), who described it as yellow needles, m.p. 208°. A specimen of this compound which had been lying for some time was found to melt at 217-218°, probably due to the formation of some acridone. A mixed melting point with the material m.p. 218-219° described above was not depressed.

IV. SUMMARY.

1. Modified Skraup reactions have been carried out on 1-bromo-, 1-nitro- and 1-chloro-β-naphthylamine. The first two compounds yielded angular 5:6-benzquinoline, the bromine and the nitro group being completely eliminated. 1-chloro-β-naphthylamine yielded 9-chloro-1-azanthracene, but in poor yield. Somewhat similar results were obtained when 5-bromo- and 5-chloro-6-aminoquinoline were submitted to Skraup reactions. p-Phenanthroline was isolated in both cases, the bromine and chlorine being partially eliminated, but whereas 9-chloro-1:5-anthrazoline was finally obtained pure, the halogen-containing compounds isolated from the experiments on 5-bromo-6-aminoquinoline were found to be mixtures of p-phenanthroline and 9-bromo-1:5-anthrazoline.

2. The application of the Combes' reaction to various amines has been investigated. 1-Bromo- and 1-chloro-β-naphthylamine condensed smoothly with acetyl acetone, and gave good yields of 9-bromo- and 9-chloro-2:4-dimethyl-1-azanthracene on cyclization. 1-Nitro-β-naphthylamine

and 5-bromo- and 5-chloro-6-aminoquinoline failed to condense with acetyl acetone. 6-Aminoquinoline did form an anil, but attempts to cyclize this intermediate compound resulted either in hydrolysis or sulphonation.

3. 1-Nitro-β-naphthylamine condensed with ethoxymethylene malonate to form two products - ethyl-β-(1¹-nitro-2'-naphthylamino)-α-carbethoxy acrylate, and a compound composed of two molecules of the amine and one of malonate. 1-bromo-β-naphthylamine and 5-chloro-6-aminoquinoline condensed with ethoxy methylene malonate giving ethyl-β-(1¹-bromo-2'-naphthylamino)- and ethyl-β-(5¹-chloro-6¹-quinolylamino)-α-carbethoxy acrylate, but attempts to cyclize these compounds failed.

4. Attempts to replace the bromine atom of 9-bromo-2:4-dimethyl-1-azanthracene by a diethylaminoethylamino side chain yielded a compound which may be bis-(2:4-dimethyl-1-azanthracyl)-ethylamine or its tetrahydro derivative.

5. Attempts to replace the bromine atom of 9-bromo-2:4-dimethyl-1-azanthracene by an amino group by heating this compound with concentrated ammonia in a sealed tube yielded a variety of

compounds, depending on the temperature used. The main product of the reaction was a compound which analysed in accordance with its formulation as bis-(2:4-dimethyl-1-azanthracyl)-amine.

6. All attempts to prepare 1-iodo-β-naphthylamine proved unsuccessful, the acid hydrolysis of the acetyl derivative, as recommended by Willstaedt and Schreiber (1934), resulting in the complete removal of the iodine.

7. 5:6-, 5:7-, 5:8- and 5:9-dichloro-2:3-benzacridines have been prepared by condensing 3-chloro-2-naphthoic acid with o-, m- and p-chloroaniline, and ring closing the products with phosphorus oxychloride.

8. In order to identify the 5:6- and 5:8-isomers, 1-bromo-5:8-dichloro-2:3-benzacridine was prepared by the ring-closure of 4-chloro-2-(1^{1}-bromo-β-naphthylamino)-benzoic acid with phosphorus oxychloride. All attempts to remove the bromine atom to form 5:8-dichloro-2:3-benzacridine have been unsuccessful.

9. 1:5:8-trichloro-2:3-benzacridine was obtained as a by-product in the ring closure of 4-chloro-2-(1^{1}-bromo-β-naphthylamino)-benzoic acid with

phosphorus oxychloride, the bromine of the corresponding bromo-acridine being partially replaced by chlorine. Attention is directed towards a number of analagous cases in aromatic bases in which bromine has been replaced by chlorine on treatment with phosphorus oxychloride, e.g. a number of pyridoacridines, prepared by Hutchison and recorded in his Ph.D. thesis (1946), and also during the present work.

10. 1:5:8-trichloro-2:3-benzacridine was prepared by the ring-closure of 4-chloro-2-(1^{1}-chloro-β-naphthylamino)-benzoic acid with phosphorus oxychloride.

11. This compound was also obtained by treatment with a suitable proportion of phosphorus pentachloride of the lower melting isomer (m.p. ~~180~~-180.5°) obtained in the ring-closure of 3-(m-chloroanilino)-2-naphthoic acid, which was therefore identified as 5:8-dichloro-2:3-benzacridine. The isomer melting at 231-2° was therefore 5:6-dichloro-2:3-benzacridine.

12. Attempts to replace the 5-chlorine atom of 5:6-, 5:7-, 5:8- and 5:9-dichloro-2:3-benzacridine by basic side chains yielded small

amounts of oily products. 7-chloro-5-(diethylaminoethylamino)-2:3-benzacridine, which crystallised as its oxalate, has so far been the only definite compound isolated.

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